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Cerebral Blood Flow Velocity
Variability in Very Low
Birthweight Infants

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A thesis submitted in partial fulfilment
of the requirements for the degree of
Doctor of Medicine, the University of
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LIST of ABBREVIATIONS

ACA	Anterior cerebral artery
AF	Anterior fontanelle
AUTVC	Area under the velocity curve
BWt	Birthweight
BPV	Blood pressure variability
BP	Blood pressure
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CBFVV	Cerebral blood flow velocity variability
CBV	Cerebral blood volume
CLD	Chronic lung disease
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CSA	Cross-sectional area
CV%	Coefficient of variation expressed as a percentage
CVR	Cerebral vascular resistance
CP	Cerebral palsy
CPP	Cerebral perfusion pressure
CSA	Cross-sectional area
CT	Computerised tomograph
CVP	Central venous pressure
CW	Continuous wave (Doppler)
ECMO	Extracorporeal membrane oxygenation
EDFV	End-diastolic flow velocity
ELBW	Extremely low birthweight

EM	Electromagnetic
FFT	Fast Fourier Transform
GA	Gestational age
HIE	Hypoxic ischaemic encephalopathy
HR	Heart rate
HRV	Heart rate variability
ICH	Intracranial haemorrhage
ICP	Intracranial pressure
IPH	Intraparenchymal haemorrhage
IPPV	Intermittent positive pressure ventilation
IUGR	Intrauterine growth retardation
IVH	Intraventricular haemorrhage
MAP	Mean arterial pressure
MABP	Mean arterial blood pressure
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
NIRS	Near infra-red spectroscopy
NICU	Neonatal intensive care unit
NMR	Neonatal mortality rate
PaCO₂	Arterial partial pressure of carbon dioxide
PaO₂	Arterial partial pressure of oxygen
PCA	Postconceptional age
PDA	Patent ductus arteriosus
PET	Positron emission tomography
PI	Pulsatility index
PNS	Parasympathetic nervous system
PVH	Periventricular haemorrhage

PVHI	Periventricular haemorrhagic infarction
PVL	Periventricular leucomalacia
PW	Pulse wave(Doppler)
rCBF	Regional cerebral blood flow
RD	Respiratory distress
RI	Resistance index
RDS	Respiratory distress syndrome
RSA	Respiratory sinus arrhythmia
SD	Standard deviation
sec	seconds
SEH	Subependymal haemorrhage
SNS	Sympathetic nervous system
SPONT RESP	Spontaneous respiration
SPSS	Statistical Package for the Social Sciences
TCD	Transcranial Doppler
VENT	Ventilation
VLBW	Very low birthweight
VMS	Ventrolateral medullary surface
WMD	White matter damage
¹³³ Xe	¹³³ Xenon

Abstract

Short-term variability in cerebral blood flow velocity (CBFV) in the VLBW infant largely relates to respiratory influence. Extreme variability may be a poor prognostic indicator. Few have studied cohorts of babies in this regard.

I sequentially studied a consecutive cohort of unselected VLBW infants, to determine the frequency of respiratory influence on CBFV and to identify factors associated with its occurrence. Doppler CBFV, arterial BP and respiratory signals were recorded simultaneously and spectral analysis was applied to identify a respiratory signal in BP and CBFV traces.

Respiratory associated variability was present in the cerebral circulation at some time in more than half of the infants studied and was most likely in those of lowest gestational age who were hypotensive. Mortality, and cerebral morbidity as assessed by cerebral ultrasound were more common in those demonstrating a respiratory influence in CBFV.

There was a strong correlation between the coefficient of variation (CV%) of BP and that of CBFV. Babies demonstrating hypotension had higher CV% in CBFV; those who did not survive showed higher variability than survivors, but there was a wide spread of values in both groups. Where the variability in CBFV was high, correlation between CBFV and BP was greater. However, no significant association was found between CV% of CBFV and brain injury, ductal patency, or sedation. Although exaggerated beat-to-beat variability in CBFV was an adverse prognostic indicator, absence of variability carried the worst prognosis.

Slow variations of cerebral blood flow velocity at a frequency of 1-5 cycles per minute, previously described as a normal phenomenon, were also examined. Evolution of this variability was studied amongst those present for a month or more. Slow variations diminished with both increasing postnatal and postconceptional age, perhaps representing maturation of the balance between the two components of the autonomic nervous system. The cycle length of the slow variations was variable suggesting the presence of several low frequency components; longer recordings would be needed to resolve these.

Addition of serial Doppler measurements of CBFV performed in the first week of life, did not improve prediction of an 18-month outcome obtained from ultrasound imaging alone.

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CHAPTER I. Introduction

I.I. Mortality and morbidity in preterm infants

Very low birthweight infants, ie those born weighing less than 1501 grams, comprise less than 1% of live births. Figures from the Australian and New Zealand Network (Donoghue et al 1999, 2000) show that of 305,923 livebirths in 1999 and 306,241 in 2000, 0.90% and 0.92% respectively were VLBW infants. However, these infants generate the major workload for Neonatal Intensive Care Units since their incidence of mortality and morbidity is much higher than that of term infants, and they usually occupy NICU beds for many more days than term babies. Prior to the 1960s, NICUs were virtually nonexistent, and in the 40s and 50s there were very few VLBW survivors. Mortality in the VLBW infant has been declining for over 40 years. Kitchen et al (1992) report an increase in survival of VLBW infants from 37.1% for the years 1966-1970 prior to the introduction of assisted ventilation, to 67.8% for the years 1980-1982. Current figures from Donoghue et al (1999, 2000) show survival to discharge of 91.5% in 1999 and 88.4% in 2000. The majority of survivors amongst the VLBW are from the higher gestational ages and birthweights. The survival rate to discharge for those born weighing less than 1kg was 74.1% for 1998 and 75.1% for 1999.

However, concern has arisen that this decline in mortality has been accompanied by a higher incidence of neurodevelopmental disability in the survivors. Major causes of death and later disabilities are respiratory distress syndrome progressing to chronic lung disease, and intracranial insults which include haemorrhagic lesions, ischaemic lesions

and infections, all of which may lead to neurological impairment. Since the introduction of surfactant administration in the early 80s to 90s, mortality but not morbidity has been significantly reduced in the VLBW infant (Bregman 1998).

Skidmore et al (1990) demonstrated a rate of neurological impairment of 29% in VLBW babies with chronic lung disease (ie those requiring oxygen for 28 days or more), compared with a rate of 9% for those requiring oxygen for 3-27 days. Those with CLD had a significantly lower mean birthweight and gestational age and a greater incidence of grade 3-4 ICH than the others. After the introduction of surfactant, Singer et al (1997) conducted a prospective longitudinal study and again found that VLBW babies with CLD performed more poorly in motor skills at all ages up to 3 years, even after control for other risk factors. Those with CLD also had higher rates of mental retardation associated with greater neurological and social risk. This supports findings from previous smaller less well-controlled studies followed up for shorter periods (Teberg et al 1991, Bregman et al 1992). Physical and neurodevelopmental impairments are obviously difficult to evaluate independently, and physical impairment alone will not be considered in detail here.

Neurological handicap remains the most adverse outcome for parents and society in general. Major disabilities include deafness, blindness, a developmental quotient of less than 2 standard deviations below the mean, and severe cerebral palsy. The term cerebral palsy describes a variety of syndromes with non progressive motor handicap. VLBW neonatal survivors are

known to have a 50 fold increase in risk of this condition, ie an incidence of 50:1000 (Pharoah et al 1998). Data from this group, collected for the years 1984-9 give a birthweight specific CP prevalence of 1.1 per 1000 neonatal survivors in infants weighing 2500 grams or more at birth compared to a prevalence of 78.1 per 1000 survivors in infants weighing less than 1000 grams at birth. The overall CP prevalence was 2.1 per 1000 neonatal survivors.

At 5 year follow-up, rates of CP remained unchanged between cohorts of VLBW infants born in 1980-82 (7.5% of a total of 222 live births) and in 1992 (7.8% of 202 live births), despite an increase in survival from 68% to 82% (Doyle et al 2000). The survival rate increased proportionally more in those with BWT between 500-999 grams than for those at 1000-1499 grams and this was especially true for those less than 750 grams. The rate of CP in survivors was also higher in those born at less than 1kg in both this study and that of Pharoah et al (1990). The severity of CP was unchanged over time.

Cooke et al (1999), found a significant fall ($p=0.046$) in the prevalence of CP in VLBW infants at 3 year follow-up, from 10.9% for the period 1982-1989 (1201 infants) to 7.3% for 1990-1993 (521 infants). This decrease was attributed to the use of antenatal steroids and postnatal surfactant.

O'Shea et al (1998) found that the prevalence of CP amongst VLBW survivors fell from 11.3% in 1982 to 9.2% (1988-1990) to 5.2% between 1992 and 1994. Mortality fell from 36.8% for 1982-4 to 13.8% for 1992-4. When adjusted for use of surfactant, the trend in mortality was no longer significant but the trend for fall in rate of CP persisted.

The percentage of cases having CP who are of normal birthweight is held to be between 53% (Cummins et al 1993) and 64% (Rosen et al 1992) so the increased survival of LBW and ELBW children with CP has not significantly altered the overall incidence.

As mentioned, in the study by Singer et al (1997), CLD was a significant independent predictor of poorer motor outcome, but mental retardation was associated with greater neurological and social risk. In a prospective multicentre trial, Vohr et al (2000) reported outcome at 18-22 months corrected age. They found that increased neurodevelopmental morbidity in the ELBW infant was associated not only with CLD, but also with grade 3-4 IVH, PVL, necrotising enterocolitis, male gender and postnatal steroid use. Decreased morbidity was seen not only with increasing birthweight but also with higher maternal education and white race. Miceli et al (2000) found prematurity and VLBW were indirectly related to early developmental outcome but by 36 months of age, outcome was more closely related to aspects of early social environment than to early physiological factors. These findings are consistent with previous reports showing that social and environmental factors significantly impact on outcome (Weisglas-Kuperus et al 1993, Monset-Couchard et al 1996).

I.I.I. Variations in the reporting of outcome studies

Many confounding variables surround the interpretation of outcome studies. These variables are inclusive of differences in populations studied, the defined groups, definition and inclusion of outcome data, the developmental tests employed and

the experience of the examiners, as well as duration and completeness of follow-up.

Studies may be based on a hospital population or a geographical population; most reports of follow-up data come from centres with a major or specific interest in perinatal care, so hospital-based population studies give a poor indication of morbidity and mortality for the overall population. Different hospitals have different referral systems and antenatal booking systems, and different neonatal units have variable levels of specialisation. Studies which are based on a geographical population are more representative of the community, but have more difficulties with regular follow-up data.

Also, different grouping of birthweights and of gestational ages have been used in follow-up reports of low birthweight infants, making comparisons difficult (Table 1). Since the introduction of early ultrasound scans, gestational age is the more reliable measure; if birthweight is used to group babies, any study performed may include more mature babies who are small for gestational age.

Table 1. Follow-up data for preterm infants

First Author	Year	Birth year (s)	No	Design	Population (Grams)	NMR%	Major H'caps	Follow-up Rate%	Follow-up
Doyle	2001	79-80	88	Geographic	<1000g	25%	14%	90%	14 Yr
Doyle	2001	91-92	401	Geographic	23-27wk	43.9%	6.8%	98.2%	5 Yr
Vermont - Oxford	1993	1990	2961	Multicentre	<1500g	15%			
Hack	1996	82-88 90-92	166 114	Hospital based	500-750g	77% 57%	MDI<70 20%	90% 87%	20mth
Regev	1995	87-92 87-90	282 114	Hospital based	<1500g <1500g	25.2%	13%	95.7%	2 Yr
Grogaard	1990	76-85 81-85 76-80	908 1011 1919		<1501g <1501g <1501g	26% 23.2% 31.1%	18% 12.1% 27.2%	45% 49.1% 39.5%	12-24 mth

Another major source of confusion arises from outcome criteria, especially the definitions of major and minor handicap. Controversy exists concerning the inclusion of epilepsy and shunted hydrocephalus; the former may be severe enough to qualify as major disability, and the latter may invoke no disability (Ventriculomegaly Trial Group 1990).

Classifications in different domains are important in the evaluation of causation, the effect of interventions, and longterm outcomes (Peterson et al 1998). Similarly, well validated, reproducible, comparable tests of disability at similar ages and performed by skilled operators, are all important elements (Aylward et al 1989). Problems surround the testing of children who are too neurologically impaired for conventional tests; this has been tackled by Amiel-Tison and Stewart (1989).

Many groups omit important outcome results. In a meta-analysis of 98 multiple outcome studies of VLBW infants (Escobar et al 1991), the incidence of cerebral palsy was reported by only 76%, blindness by 71%, deafness by 62% and the occurrence of sudden infant death syndrome by 48%. Only 37% presented data from comparison groups (eg matched groups of infants born at term), and only 33% tried to achieve impartial assessment.

Duration of follow-up needs to be at least 9 months to establish the diagnosis of cerebral palsy, and for absolute certainty 2 years is required. Even then, Kitchen et al (Victorian Infant Collaborative Study Group 1991) claimed that a 2-year evaluation of the ELBW (ie <1000gm) infant is often unduly pessimistic. The calculated rate of severe

disability in his cohort of 351 ELBW babies was 22.5% at 2 years, 19% at 5 years and 18% at 8 years. The predominant explanatory factor was a change in the psychological test results.

Major longterm sequelae of PVHI are spastic hemiplegia and intellectual deficits (Volpe 1997). The lower extremities are affected as much as the upper, presumably because of the periventricular locus of the lesion. Major longterm problems associated with PVL include spastic diplegia, the major motor deficit seen in preterm infants. The lower limbs are generally more affected than the upper because of necrosis in the periventricular regions where the white matter is traversed by descending fibres from the motor cortex. Severe lesions with lateral extensions may also affect the upper limbs and intellect (Fazzi et al 1992, Wiesglas-Kuperus et al 1992). Powell et al (1988 1 and 11) have shown different associated antecedent variables for spastic diplegia and hemiplegia in a large cohort of preterm infants <2001 grams. In Powell et al's data there was a trend towards increased numbers with hemiplegia where more extensive IVH (grades 3 and 4) existed. Grouping all cerebral palsy together may miss this important association, but in many studies the numbers are too small to categorise cerebral palsy and show significant differences.

Information concerning late deaths is also required for the accurate calculation of the prevalence of handicap amongst survivors. The handicap rate amongst live births is impossible to obtain since many do not survive long enough for evaluation.

In summary, the mortality of VLBW infants has been greatly reduced over the past 40 years but morbidity has remained

relatively constant around 6-8% despite a falling mortality rate. Interpretation of follow-up results has been greatly hampered by factors including diversity of definitions of population, inclusion birthweight and severity of handicap, the method and timing of assessment, and duration and completeness of follow-up.

Research from the past 2 decades has concentrated on ways to prevent impairment in the VLBW population.

I.II. Cerebral injury in the very low birthweight infant

I.II.I. Categories of intracerebral injury in the VLBW infant

Cerebral injury in the VLBW baby has traditionally been separated into 2 categories, namely haemorrhagic and ischaemic. However, these injuries are closely related and may overlap or coincide. They may in fact be different manifestations of the same pathological process. From the perspective of prognosis, white matter damage is by far the most important lesion and a better classification of damage might create 3 general categories, namely : white matter damage(WMD), haemorrhage in non-parenchymal areas of the brain, and lesions in other brain locations including basal ganglia, brain stem, etc(Paneth 1999).

White matter damage includes such lesions as cystic PVL, haemorrhagic infarction and others known only from pathological examination such as rarefaction, hypertrophic astrocytes etc(Gilles et al 1998).

The classification into haemorrhagic and ischaemic lesions as found below has been included, however, because until now most data concerning incidence of damage and outcome are based on these classifications.

Sinha et al(1985) found that 12.3% of 219 infants less than 33 weeks gestation had both intracranial haemorrhage and periventricular leucomalacia, and Grant(1986) showed that of 26 consecutive cases of PVL in infants of 34 weeks gestation or less, 6 had significant haemorrhage and small amounts of blood were seen in most of the other 20. More recently, Kuban et al(1999) found that the development of WMD abnormalities appears strongly associated with IVH especially where ventriculomegaly(VM) is also present. In groups at all gestational ages, the presence of IVH and IVH plus VM increased the likelihood of identifying WMD. This association was most evident with medium to large lesions and where lesions were more extensive; IVH occurred in almost half of those with bilateral WMD restricted to the posterior cerebrum(a description often used to describe PVL on ultrasound).

I.II.II. Detection of intracerebral injury

The earliest method to detect intracranial injury in a preterm baby was retrospective correlation between post-mortem examination of the brain, clinical events and outcome(Papile et al 1978, Pape et al 1983). Imaging techniques became available in the late 1970s. Initially, these concentrated on normal and abnormal anatomy and cerebral injury, but more recently they have been used to gain insight into the physiology and pathophysiology of cerebral function and cerebral blood flow. Serial MRI imaging by Huppi et al(1998) and others, has demonstrated cortical development and periventricular white matter maturation in VLBW infants approaching term.

I.II.III. The role of imaging in detection and diagnosis of intracerebral insults in the VLBW infant and relationship to outcome

Computed tomography was the first form of noninvasive imaging used in live newborn infants. Papile et al (1978) prospectively examined VLBW infants. They determined the incidence of ICH, and found poor correlation with clinical events.

Since the late 1970s, ultrasonic imaging of the infant brain has been used to obtain valuable information concerning normal and abnormal anatomy and cerebral injuries (Hashimoto et al 2001, Perlman et al 2000, Murgu et al 1999, Kuban et al 1999). Magnetic resonance imaging (MRI) became available in the early 1980s in adults. Because the water content of the preterm infant brain is very high and myelination is incomplete, differentiation between grey and white matter, one of the most advantageous features of this technology, is more difficult. However, MRI can show glial reaction in the early stages of injury, as well as end-stage damage. More recently, MR studies have been performed on babies early in life, sometimes even in the first week (Maalouf et al 1999).

Anatomical landmarks identified by ultrasound on coronal, sagittal and parasagittal scans have been verified by comparison with brain slices at autopsy (Levene et al 1981, Pape et al 1983, Paneth et al 1990). With the improving resolution of ultrasound, PVL may now be diagnosed. The initial appearance is usually that of echodense lesions which probably represent glial reaction, and later the lesions become cystic. However, there is little pathological correlation to prove that

these correspond to PVL. Many studies have now been published which correlate ultrasound appearance with later outcome (Perlman et al 2000, Hashimoto et al 2001, Bozynski et al 1985, Grant et al 1986, Calvert et al 1986).

Valkama et al (2000) performed MRI studies on 51 VLBW infants at term. Neuromotor development was followed up to 18 months corrected age. Parenchymal lesions seen in MRI at term predicted CP with 100% sensitivity and 79% specificity- the corresponding figures for ultrasound were 67% and 85% respectively.

The ability of ultrasound to detect all at risk of CP or low IQ is limited. Since MRI gives a superior image, it should offer an advantage in predicting outcome. Where the aim is to detect all lesions, even those with less ominous implications, MRI is superior. However, since both MRI and ultrasound detect the most severe lesions, ultrasound remains an appropriate aid for information with which to counsel parents. The fact that preterm infants do as well as they do considering the number of lesions identified on MR, promotes the concept of the preterm brain's ability to adapt (Ment et al 2000).

Ultrasound remains a safe, noninvasive method which can readily be repeated with the machine wheeled to the cot or incubator without interrupting monitoring or assisted ventilation (see Figure 11).

Computerised tomography and MRI techniques remain less practical in the acute phase of illness since both require the infant to be moved. It is difficult to adequately monitor an infant during an MRI study (Roth et al 1985, McArdle et al 1986). It also remains difficult to interpret group differences and

putative developmental changes in regional brain volumes in infants using MRI (Peterson et al 2001). The best predictive factor for neurodevelopmental outcome still appears to be detection of PVL on ultrasound (van de Bor 1992).

Murgo et al (1999) found that ultrasound was more sensitive than early MR in detecting cystic PVL because of the transient nature of the cysts; MRI was more useful to evaluate non-cystic WM lesions.

Current literature would suggest that a combination of ultrasound, CT and MRI may be useful to determine the exact occurrence of and clinical risk factors for neurological outcome.

The incidence of periventricular-intraventricular or intracranial haemorrhage in preterm infants is now around 18-25% in most units (Table 2).

I.II.IV. Incidence of intracerebral injury in the VLBW infant

The incidence is highest at the lowest gestational ages and decreases with increasing gestation. It is an uncommon occurrence after 33 weeks gestation. The use of antenatal steroids and postnatal surfactant is likely responsible for much of the decreased incidence over the past 15-20 years (Cooke et al 1993, Jobe et al 1993).

From autopsy reports, the incidence given for PVL varies between 7% and 34% of necropsies (Banker and Larroche 1962, Armstrong and Norman 1974, Pape et al 1983 and Shuman 1980). Infants in these series had a wide range of gestational age and birthweights. The incidence from ultrasound alone or in combination with post-mortem results is seen in Table 3 below.

Table 2. Incidence of IVH/PVH in preterm infants

Year	First Author	Population GA or Bwt	Number	Incidence of ICH
1999	Donoghue	<1500gm	2750	Total 21.9% Gde3,4 6.6%
1999	Kuban	<1500gm	1605	18.4%
1998	Donoghue	<1500gm	1773	Total 24.4% Gde3,4 7.1%
1994	Cooke	<1500gm	523	SEH/IPH 31.6% IPH 5.5%
1993	Vermont-Oxford	<1500gm	2458	26%
1985	Sinha	<33wk	219	36.1%
1983	Papile	<1501gm	232	43%
1978	Papile	<1500gm	46	43%

Table 3. Incidence of PVL in preterm infants

Year	Author	Population GA or Bwt	Number	Incidence of PVL
1999	Kuban	<1500g	1607	8% with at least 1 WM abnormality
1995	Regev	<1500 g	114	8.8%
1986	Trounce	<1501 g	200 cohort	26%- PVL 13.5% - Prolonged flare 12.5%
1985	Bozynski	<1201 g	100	5% of survivors
1985	Sinha	<33 weeks	219	17.8%
1984	Nwaesei	600-720g	23, dying at >20days	52%
1985	Rushton	<2000g	216	7.9%

I.II.V. Structural basis of intracerebral injury in the VLBW infant

The majority of intracranial haemorrhages in the VLBW baby are thought to originate in the capillary bed of the germinal matrix. This is an embryonic structure which lies beneath the floor of the lateral ventricles ie in the region of the caudate nucleus and/or the caudo-thalamic notch. The germinal matrix is prominent in the very preterm infant, and involutes around 32-34 weeks gestation. From this structure, the germinal cells migrate to form the layers of the cerebral cortex and the deeper nuclear structures (Grant 1986). Migration is virtually complete by 26 weeks gestation and at this stage the germinal matrix is highly vascular with a poorly supportive connective tissue network, and so is extremely vulnerable to haemorrhage.

With the disappearance of the germinal matrix at 32-34 weeks, there are changes in the pattern of cerebral vasculature along with rapid growth of the cortex and white matter. To provide the greatly increased vascular requirements for these regions, the cortical vessels proliferate. By term, there is a well-developed arterial supply to the cortex. In the preterm infant, the regions most susceptible to hypoxic-ischaemic insult are the arterial watershed areas adjacent to the external angles of the lateral ventricles (Wigglesworth and Pape 1978); the most frequent distribution of this type of injury includes the periventricular white matter adjacent to the frontal horns, the external angles of the lateral ventricles and the lateral surfaces of the occipital horns, which receive flow from the end arteries of the anterior and middle and the

middle and posterior cerebral arteries. Cerebral infarcts in these regions were first described by Virchow in 1867 but the term periventricular leucomalacia was not used to describe them until 1962 when Banker and Larroche proposed the relationship with vascular border zones.

The earliest stage of PVL is characterised on ultrasound by areas of increased echodensity in the periventricular white matter, usually near the external angle of the lateral angle of the lateral ventricle (Maalouf et al 1999, Grant et al 1986). This ultrasonic appearance has been confused with the normal echogenic periventricular halo (Grant et al 1983, Laub 1986), and remains controversial, though less so as ultrasound imaging improves technically. Levene et al (1983) suggest however, that the forerunner to PVL can be recognised by its presence in both coronal and sagittal planes, its tendency to extend more anteriorly than the "normal halo", and its persistence or progression. Graham et al (1987) found a slightly increased risk of handicap where "flare" had persisted for 2 weeks. Appleton et al (1990) however, found handicap in 26% of survivors who had isolated and transient "flares" seen in the neonatal period.

In the progression to PVL, these echodense regions may undergo cavitory necrosis and develop into cysts which become well-defined and may enlarge. Classically, grade 4 IVH, which also usually cavitates, is described as remaining in communication with the ventricle. These issues may well be clarified by further MRI studies.

Using ultrasound, haemorrhagic injury has been categorised as uncomplicated germinal layer haemorrhage (grade 1 or sub-

ependymal haemorrhage), haemorrhage into the ventricular space with (grade 3) or without ventricular dilatation (grade 2) and haemorrhage into the parenchyma of the brain (grade 4), (Papile et al 1978; Levene et de Crespigny 1983). Controversy exists regarding ventricular enlargement (VE) and intraparenchymal blood. Ventriculomegaly and hydrocephalus have traditionally been interpreted as sequelae of IVH. Increasing evidence, both pathological, which demonstrates that WMD is often present in infants dying of VE (Paneth et al 1990), and prognostic, showing that those with VE have risks of abnormal development similar to those with WMD (Ventriculomegaly Trial Group 1990), suggests otherwise.

Leviton et al's work (1996) supports the view that VE is best considered as WMD. Further support comes from ultrasound. Kuban et al (1999) could differentiate only 53% of 1607 VLBW infants with WMD as having PVHI or PVL. They found that IVH and VE increased the odds by 50 times, of having medium-large parenchymal echodensities compared with those without either lesion. Intraventricular haemorrhage alone was also a risk factor for WMD though not as powerful as IVH and VE combined. This may be because IVH contributes to the WMD or simply because of shared antecedent factors.

Many neonatologists now agree that haemorrhage and small isolated IVH without ventricular dilatation is innocuous and lends the same prognosis as does a normal ultrasound (Regev et al 1995; Watt 1994; Alvarez et al 1994); any other category of haemorrhage is associated with a higher risk of handicap. A caveat to this comes from recent data from Ment et al (2000) suggesting that even those infants with low grade haemorrhage

may be at cognitive disability when compared to gestation-matched peers with no haemorrhage.

Table 4. Cases of bilateral occipital PVL and their outcome (Rennie JM:Neonatal Cerebral Ultrasound 1997 p225)

Author	Cohort size, details	No.cases	No.with CP
Weindling(1985)	124<1500gm or<34wk	8	8
De Vries(1988)	676,34wk	12	4 died 6CP 2<9mth
Graham(1987)	200<1500gm	8	8
Fawer(1987)	112<1500gm	5	5
Cooke(1987a)	798<1500gm	24	21
Monset-Couchard (1988)	471<1500gm	6	6
Hansen(1989)	1600 mostly <1500gm	16	16
Pidcock(1990)	288	20	18
Weisglas-Kuperus (1992)	79<1500gm	2	1
Fazzi(1992)	299<32wks	14	14
Pierrat(1993)	33 cases in 2 years Details not given	9	1 died 8 CP
Total	>4373	124	111

PVL is more likely to be associated with cognitive and motor defects than is a parenchymal haemorrhagic lesion or a porencephalic cyst(Costello et al 1988). The size, number and position of cysts in PVL can vary and these features are highly significant to outcome. Graham et al(1987) found that no infant

with a single small anterior cyst developed severe cerebral palsy, but that multiple, occipital cysts invariably signified a poor prognosis.

Most reported survivors with cysts confined to the frontal zone, or single unilateral cysts have been reported as normal at follow-up (Graham et al 1987, Shortland et al 1988, Fawer and Calame 1991, Fazzi et al 1992).

Of 124 cases with bilateral occipital PVL, 93% were seriously handicapped (see Table 4) (Rennie 1997). The predominant diagnosis at follow-up was cerebral palsy, either spastic quadriplegia or diplegia. Developmental delay was less often observed.

Cysts involving more than one area have a poor prognosis (Shortland et al 1988); and follow-up of children with severe PVL has shown that cerebral atrophy is not uncommon (Lou 1983).

I.II.VI. Clinical situations associated with intracerebral injury

Not surprisingly, no single cause has been found to explain the relatively high incidence of intracranial haemorrhage in the VLBW infant; however, most agree that ICH is most likely to occur in the smallest, sickest premature infants and that these individuals are subject to the most adverse events in the early neonatal period. Risk factor analyses have linked insults known to increase CBF, such as respiratory distress, pneumothoraces, rapid volume expansion, hypercarbia, hypoxaemia and seizures with GMH/IVH (Ment et al 1991, Watt 1994). Others have divided aetiologies into the prenatal and delivery period- emergency Caesarean section for FHR abnormalities, prolapsed cord or placental abruption, and

postnatal events such as symptomatic PDA and severity of lung disease (Paneth et al 1993).

Mehrabani et al (1991) found that the risk of developing a grade 3 or 4 IVH in the VLBW infant was increased almost 10 times where pneumothorax was associated with hypotension in comparison with VLBW infants who had pneumothoraces but were normotensive. Watt (1994), Bada et al (1990) and Miall-Allen et al (1989) have also implicated hypotension as an important risk factor for ICH in preterm infants. All of the above factors relate to severity of illness in the smallest, least mature babies.

Most ICH occurs within 72 hours of birth and 32-44% is already present by 4.9 ± 2.2 hours of age (Paneth et al 1993, Trounce 1986). Since haemorrhage rarely occurs after 72 hours and is even rarer after 1 week of age, although the incidence is highest in the least mature infants, postnatal factors seem to be important (Ment et al 1993). Animal data suggests postnatal induction of germinal matrix microvascular maturation (Ment et al 1991).

Risk factors for PVL are less well documented, but since both PVH and PVL may coexist (Paneth 1999, Kuban et al 1999, Weindling 1995), and both are most common in those less than 30 weeks gestation, it is probable that they share many predisposing factors, including severity of illness. Murphy et al (1996) performed autopsies on 83 babies of less than 32 weeks gestation. Thirty nine had ischaemic WMD, and the aetiology was thought to be prenatal in 12 cases. They found no clear associations between the timing of adverse clinical factors and the timing of ischaemic cerebral damage and proposed that damage

may result from a sequence of events rather than a single specific insult. Pre-eclampsia, IUGR, delivery without labour, neonatal sepsis, necrotising enterocolitis (NEC) and seizures were associated with postnatal damage. In recent years, both intra-uterine infection (Resch et al 2000, Leviton et al 1999, O'Shea et al 1998) and postnatal hypocarbic alkalosis (Fujimoto et al 1994, Graziani et al 1992) have been shown to be highly significant in the aetiology of WMD.

Zarfin et al (1984) found that while ICH can usually be diagnosed by 2 weeks, PVL is sometimes not seen till 6 weeks and cystic degeneration can occur even later. Bozynski et al (1985) first noted echodensities between 1 week and 1 month, and cavitory lesions as late as 10 weeks post-natal age; the series of Sinha et al (1985), found that ischaemic lesions first became obvious between 1 and 70 days. However, although IVH is often imaged before WMD, the 2 lesions may have begun at the same time, or WMD may have preceded the haemorrhage. Inder et al (1999) have demonstrated the presence of WMD with MRI before it was visible on ultrasound imaging. Thus, IVH may contribute to the pathogenesis of WMD, or the 2 forms of damage may be associated statistically simply because they share the same common physiological disturbances. Further studies combining different modalities of imaging techniques may clarify the relationships of different forms of damage and their pathophysiology.

In summary, cerebral injury is very common in the VLBW baby. Haemorrhagic and ischaemic lesions frequently coincide and may be part of the same pathological process. Haemorrhage occurs far more frequently and is often detected earlier than

ischaemia; PVL can be far more difficult to diagnose by scanning techniques, especially in its earlier stages. All haemorrhages other than germinal layer and simple grade 2 bleeds, carry an increased risk of neurodevelopmental handicap, but ischaemic lesions are more sinister especially when multiple and located in the occipital region.

I.II.VII. Pathophysiology of intracerebral injury in the VLBW infant

Each of the theories behind the pathophysiology of cerebral injury has been linked with systemic arterial blood pressure values and the assumption that small, sick preterm babies lack cerebral autoregulation and hence are more vulnerable to brain injury.

Cowan et al(1988) measured arterial BP and the mean cerebral arterial blood velocity obtained from Doppler, on a beat-to-beat basis in 12 premature newborn babies and found that of the 4 who had what they considered effective cerebral autoregulation, none developed haemorrhagic or ischaemic lesions; of the 2 with "impaired autoregulation" 1 had a small bleed and 1 a mild flare; and of the 6 who lacked autoregulation, 4 had large ischaemic and/or haemorrhagic lesions.

The results of Tsuji et al(2000) suggested a direct relationship between impaired cerebrovascular autoregulation and the development of haemorrhagic and ischaemic lesions in the human premature newborn. Their study employed NIRS at the cotside.

I.III. Cerebral blood flow and function - methods of assessment

There is currently no acceptable noninvasive method of assessing instantaneous change in cerebral blood flow in the human newborn.

Many different methods exist to assess CBF and cerebral function; most of these employ assumptions and have many sources of error and some are possible only for use in experimental work. Below are described some of the techniques most relevant to the human newborn with respect to both cerebral blood flow and function. Table 5 demonstrates some values obtained for cerebral blood flow or blood volume in the newborn human infant and the techniques used to measure these.

I.III.I. Radioactive microsphere technique

Organ blood flow has been measured using either radioactive or coloured microspheres, the latter having environmental and economic advantages (Hakkinen et al 1995). The microspheres become evenly distributed throughout arterial blood and the amount which reaches any tissue depends upon the perfusion of that tissue. Several injections can be made using different labels for different situations before the animal is sacrificed and radioactive counts measured from the tissue being studied. Regional CBF has been measured by injecting radioactive microspheres into the left ventricle. It is possible to measure regional flow to tissue segments of 0.2-0.5 grams. This has been taken as a gold standard of CBF but of course is feasible only in animal studies (mostly newborn piglets and lambs). In newborn piglets, this has been used to assess cerebrovascular responses to drugs such as

indomethacin(Pourcyrous et al 1999), and to such situations as haemorrhagic hypotension(Anwar et al 1996). Comparative studies have been performed using NIRS(Goddard-Finegold et al 1998), and Doppler ultrasound(Martin et al 1990) for validation of those techniques.

I.III.II. $^{133}\text{Xenon}$ technique

This has been widely used to measure CBF in humans and several studies have been performed in the newborn. Xenon can be given intravenously via the carotid artery, or by inhalation. Xenon is a freely diffusible inert tracer and this method again is based on the Fick principle. Xenon is detected, however, by means of gamma emissions. This is a complex method employing many assumptions which are not necessarily true, and with many possible sources of error. The technique assumes that concentration in tissue at any time is proportional to concentration in venous blood, expressed by the blood-brain partition coefficient, although this may not be true for high perfusion rates. Because Xenon is highly lipophilic, the extent of myelination must be considered in measuring the blood-brain partition coefficient; Greisen in 1986 used a measurement for newborn infants derived from homogenate from neonatal post-mortem material. Using a weighted mean of the fast(grey matter) and slow (white matter) compartments of the deconvoluted decay curve(Greisen 1986) helps minimise error arising from the different rates of flow to grey and white matter.

Xenon does recirculate to some extent; this can be partly compensated for by counting gamma emissions over the lungs since alveolar air will equilibrate with pulmonary capillary

blood, but this does not take account of intracardiac and intrapulmonary shunts. The cumulative radioisotope dose limits the number of measurements made.

Comparisons of values of CBF obtained by NIRS and by the ^{133}Xe technique show the difference to be close to zero in the low range of CBF, but NIRS may underestimate CBF in the high range (Skov et al 1991).

Currently, Xe studies have largely been superceded by other technologies, but one group has recently studied regional differences in resting CBF in infants less than 34 weeks gestation (Baenziger et al 1995), and another has studied the effects of oxygen at birth on cerebral vasoconstriction in the preterm infant (Lundstrom et al 1995).

Table 5. Measurement of cerebral blood flow/volume in the newborn human infant

Method	First Author (year)	Infant details	Numbers	CBF ml/100g/min	CBV ml/100g	Comments
NIRS	Tyszczyk (1998)	GA 27.5 (24-34) wks	14	13.9 (± 6.9)		MABP < 30mm
		GA 27.5 (24-34) wks	16	12.3 (± 6.4)		MABP \geq 30mm
NIRS	Wyatt (1990)	GA 25-41 wks	12		2.22 \pm 0.4 (SD)	Normal brains
		GA 24-42 wks	10		3.00 \pm 1.04 (SD)	Brain injury
PET	Altman (1988)	GA 26-36 weeks	16	4.9 - 23		No significant relationship between mean CBF and outcome
		2 HIE				
		GA Term		9 - 73		
NIRS	Edwards (1988)	GA 25-44 weeks	11 babies	7 - 33		CV% within babies 12-25%
			31 studies			
¹³³ Xe	Greisen (1986)		11		19.8 (± 5.3 SD)	No RD
			9		21.3 (± 12.0 SD)	CPAP
			24		11.8 (± 3.2 SD)	IPPV
¹³³ Xe	Younkin (1982)	Normal preterm	15	42		3 days old

I.III.III. Positron emission tomography (PET)

Where studies using CT and MRI show anatomical imaging, PET can detect functional disturbances in the brain so is known as functional imaging.

This is also a non-invasive procedure which takes advantage of the unique properties of annihilation radiation that is generated when positrons are absorbed in matter, to provide an image that is a highly accurate representation of the radionuclide at a selected plane through the organ. This technique requires a positron emission tomograph to accurately measure the administered radioactivity in vivo, a cyclotron or linear accelerator to generate the positron-emitting radionucleotide and mathematical models of radiotracer kinetics that relate tissue radioactivity measured by PET to a quantitative value such as CBF. Isotopes commonly used in PET have a half-life of minutes to hours so the cyclotron must be close by.

In the newborn human brain, PET has primarily been restricted to measurements of CBF and cerebral glucose metabolism (Chugani 1998, Altman et al 1991). Altman et al (1988) used PET to show that in the newborn infant, unlike adults, CBF values of less than 10ml/100grams/minute can lead to a normal neurodevelopmental outcome, and one group studied brain oxidative metabolism after inducing aphyxia in newborn piglets (Bauer et al 2000, Brust et al 1999).

Recent studies have employed a relatively new technetium-^{99m} ethylcysteinate dimer (^{99m}Tc^m-ECD) single photon emission CT (SPET) at term to predict neuromotor deficits at the corrected age of 18 months in VLBW infants (Valkama et al 2001). The

sensitivity of SPET in predicting moderate or severe CP (7 infants) was 100% and the specificity 67%. The corresponding results for ultrasound were 71% and 74% respectively, so SPET can predict the most severely affected well, but not all mild cases.

I.III.IV. Kety-Schmidt technique

The Fick principle states that the rate of any substrate uptake or output by or from an organ equals blood flow to the organ times the difference in substrate concentration between arterial and venous supply. Global CBF may be measured using a modification of the Fick principle, as described by Kety and Schmidt (1945). This entails administration of stable nitrous oxide gas and frequent sampling from both arterial and jugular venous blood. As brain tissue becomes saturated with the gas the cerebral venous concentration approaches the arterial concentration. With a knowledge of the brain:blood partition coefficient for nitrous oxide, CBF may be calculated from the rate of fall in the arterio-venous difference. This method disregards connections between intracerebral and extracerebral blood supplies, assumes a constant partition coefficient and supposes that equilibration between jugular venous blood and brain tissue occurs within 10 minutes. It is possible to monitor cerebral metabolism by combining the cerebral metabolic rate for oxygen and cerebral lactate production measured from the arteriovenous differences. No neonatal studies have been performed using this technique.

I.III.V. However, **near-infrared spectroscopy** is a noninvasive method which measures the proportion of oxygenated and deoxygenated haemoglobin and allows calculation of absolute

values of cerebral blood flow and cerebral blood volume. Oxygenation in blood and tissue of the brain can be monitored by measuring the absorption of light in the wavelength 700-1000nm through the brain. Cytochrome a, a_3 is the terminal member of the respiratory chain which accounts for more than 90% of oxygen utilisation in cellular respiration. Within the NIR spectrum, cytochrome a, a_3 and haemoglobin are the only natural compounds absorbing NIR light which react to changes in oxygenation. Thus to ascertain the contribution of one, the light absorbance of the other must be determined. Changes in the concentration of cerebral oxygenated and de-oxygenated haemoglobin can be measured, and hence cerebral blood volume calculated (Rolfe et al 1992). Indocyanine green (ICG) can be used in place of haemoglobin as it strongly absorbs near-infrared light and is rapidly cleared from the body (Patel et al 1998). Cerebral blood flow may be calculated using a modification of the Fick principle. In neonates this may be performed by the cotside where light at several different wavelengths is transmitted from a fibre optic light source through the infant head.

Certain assumptions must be made to get absolute values for CBF and CBV, that: the brain is optically homogeneous, Hb is in a constant spatial distribution within the brain, the haematocrit within the brain is stable throughout each NIRS study, global CBF and O_2 consumption are stable during small transient changes in arterial saturation, and cerebral transit time in the newborn is around 8 seconds. The validity of CBF and CBV measurements is hard to establish, but the published ranges for CBF and CBV have been fairly consistent and further studies may help give standard values in term and preterm

newborn populations. Near-infrared spectroscopy may also aid in the identification of infants at risk of neurologic impairment following subclinical ischaemia (Brazy et al 1985, 1988), and help define physiological responses to clinical interventions (Wyatt et al 1989, 1990). Its usefulness in clinical medicine should become clearer when NIRS technology improves (Adcock et al 1999).

I.III.VI. Magnetic resonance imaging

Magnetic resonance imaging is based on the principle that atomic nuclei in the body with an uneven number of protons and neutrons, have a magnetic moment or spin. Hydrogen is the most abundant and strongest of these nuclei and is ideally suited for MRI. A radiofrequency pulse from a transmitter coil, orientated perpendicular to the long axis of the main magnetic field, is applied to hydrogen nuclei or protons allowing a signal to be generated for subsequent image construction. This allows multiplanar viewing, gives unparalleled contrast resolution, and avoids the need for ionising radiation. Quantitative methods have been devised, and applied as post-processing computer techniques for conventional MRI studies. MRI can not only precisely differentiate grey matter from white matter, but also myelinated from unmyelinated white matter. This allows in vivo assessment of brain maturation.

Currently, most would combine ultrasound and MRI studies to gain as much information as possible concerning neurological development, damage and prognosis in the VLBW infant (Murgo et al 1999, Ment et al 2000, Peterson et al 2001, de Vries 1998).

I.III.VII. Doppler ultrasound

This is a noninvasive technique to assess cerebral and cardiac circulation which can be performed at the bedside. Because it can safely be repeated on numerous occasions it is particularly suited to longitudinal studies. Duplex Doppler scanners, as used in this study, combine ultrasound imaging and Doppler units. Cursors on the image depict the position of the sample volume and allow a signal to be obtained from a known point at a known angle.

I.IV. Doppler ultrasound technology

I.IV.I. Doppler effect

Figure 1 demonstrates the path of an ultrasound beam in tissue. An ultrasonic Doppler velocimeter senses change in frequency imposed on an ultrasonic wave as it is reflected or scattered from a moving target. This change in frequency is given by the Doppler equation

$$f_d = \frac{2vf \cos\theta}{c}$$

where v = velocity of target (blood)

f = (ultra) sound frequency

c = speed of ultrasound in tissue

θ = angle between ultrasound beam and direction
of flow (Doppler angle)

f_d = Doppler shift in Hz

In haemodynamic studies, ultrasound is usually directed from the skin surface towards a blood vessel, and ultrasound is scattered back towards the transmitting or closely adjacent receiving ultrasound transducer.

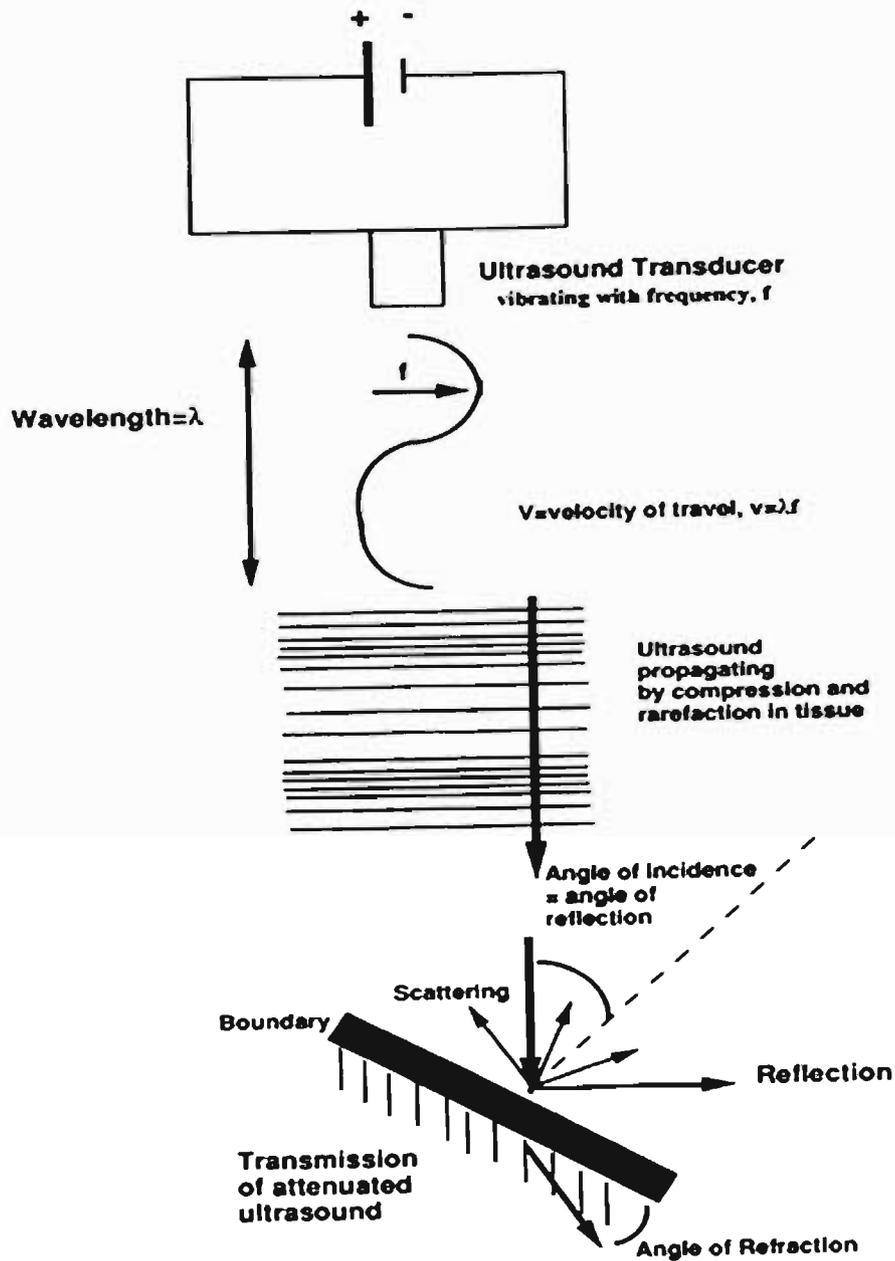


Figure 1 The path of an ultrasound beam in tissue
(Rennie JM: Neonatal Cerebral Ultrasound 1997 p225)

Transmitted and received signals are then compared and the Doppler signal is derived from the difference. It is fortuitous that at the commonly used ultrasound frequencies (2-

10MHz), and with the velocities commonly found in blood vessels, the frequency difference is within the audible range.

There are 2 distinct types of Doppler velocimeter, continuous wave, and pulse wave. Continuous wave systems use a transducer containing 2 piezo-electric crystals, 1 of which sends out a continuous ultrasound signal into the tissue. The second is used for receiving. This type of system has no depth resolution, so a returning signal may come from a vessel at any depth or from several vessels each at a different depth. This is especially true in newly born preterm infants where the distances between vessels is extremely small.

Pulse wave Dopplers usually contain a single crystal which acts as both transmitter and receiver. Ultrasound is generated in short pulses. After each pulse has been transmitted there is a short pause before a gate in the crystal opens to receive returning signals from a small tissue sample. The depth of the returning signal is calculated from the delay between transmitted and received signals. The time for which the gate is open plus the length of the transmitted pulse determine the length of the sample volume.

Aliasing is a problem peculiar to pulsed Doppler instruments. Range-gated duplex systems are only able to detect velocities up to a finite maximum and very fast moving particles may pass through the area of sampling between transmission of successive pulses if the gap is too long, being missed altogether by the sampling beam. Signals need to be sampled at least twice per cycle of their highest frequency component in order to unambiguously resolve that component. If

the sampling frequency is too low, then the frequency of the sampled signal is in error as shown in Figure 2.

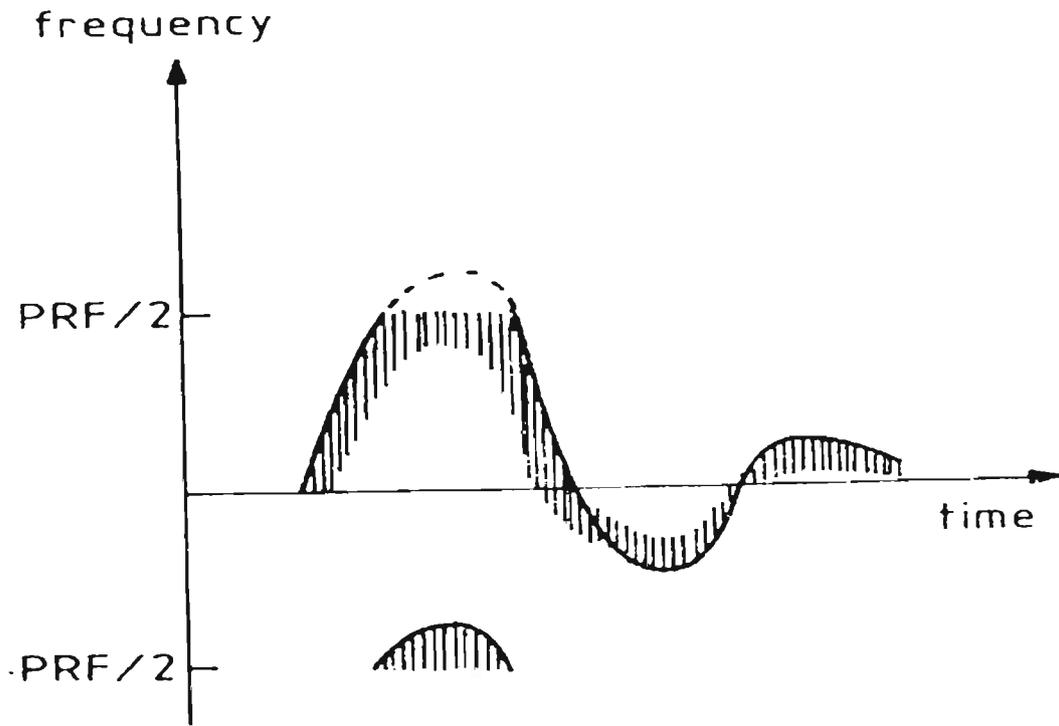


Figure 2 Real-time spectrum with aliasing

Also, in a direction-resolving pulsed Doppler instrument, the direction of flow is falsely indicated. Thus the highest Doppler shift frequency that the pulsed Doppler instrument can measure is equal to half the pulse repetition frequency of the instrument, known as the Nyquist frequency. If Doppler frequencies above this limit are present, they will be displayed as spurious frequencies equal to the Doppler shift minus the pulse repetition rate. They will appear within the limits plus or minus half the pulse repetition frequency and changed in sign. This is demonstrated in Figure 3 below.

Aliasing is rarely a problem for the velocities found in the peripheral arteries in the newborn. High pulse repetition

frequencies introduce multiple gates (ambiguity of range) and increase the ultrasound dose received by the studied tissue. However, for studies of fetal and neonatal brain, where insonating the wrong vessel is a distinct possibility, PW is usually the preferred system.

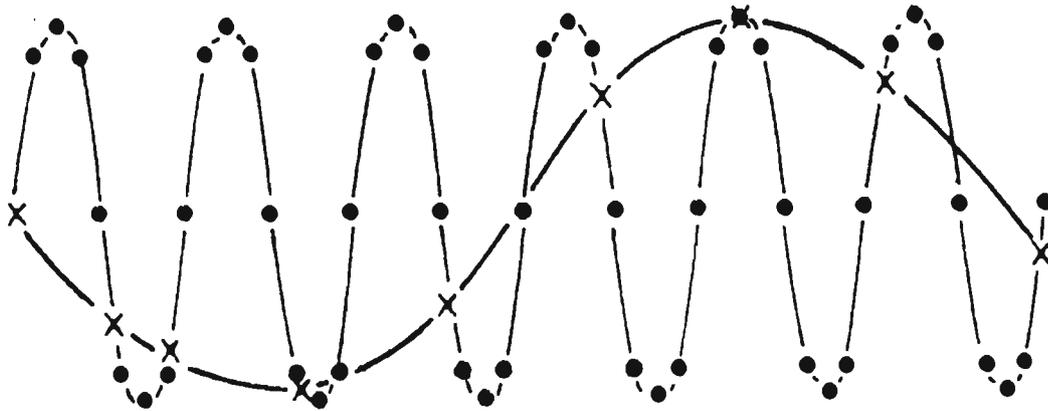


Figure 3 Aliasing

Shape and frequency of the sampled signal is preserved when the signal is sampled at a sufficiently high frequency (\bullet). The frequency of the reconstructed signal is erroneously low when the signal is sampled at too low a frequency (X).

Lateral resolution is obviously of major importance when imaging has priority, but for Doppler applications optimal results require only enough resolution to obtain a signal from a vessel without noise from adjacent structures or vessels. Further narrowing of beam width will limit spread of ultrasound across the vessel diameter giving uneven representation of all velocities within the resultant Doppler signal; this is especially important for volumetric flow measurements.

Using Doppler ultrasound, flow(Q) can be derived from the formula

$$Q = \text{velocity} \times \Pi r^2$$

where r = the radius of the vessel examined.

Most clinicians believe that volume of flow would be the most informative parameter to measure, but current technology does not permit accurate measurement of the size of small neonatal cerebral arteries. Therefore characteristics of the Doppler signal have been sought which reflect change either proportional to that of volume flow or CBFV resistance.

Most Doppler machines incorporate a high-pass or vessel wall filter. As well as ultrasound scatter from red cells within a blood vessel, vessel wall movement produces a low frequency, high power Doppler signal and it is this which is filtered out. Otherwise falsely low mean velocity and volumetric blood flow calculations would be obtained. Excessive high-pass filtering may remove the signals from the very low velocity blood flowing close to the vessel wall and give an overestimate of mean velocity and volumetric blood flow. If the frequency of the Doppler signal in diastole lies below that of the filter, diastolic velocity will be recorded as zero which may significantly affect pulsatility and resistance indices. Using a smaller Doppler angle minimises the effect of wall thump by maximising Doppler shift from red blood cells and minimising shift from wall movement.

Blood flowing within a vessel moves at different velocities, that in the centre generally having a higher velocity than that at the periphery. The plot of the velocity across a vessel is known as the velocity profile and this

varies with the size of the vessel and with the cardiac cycle. In large vessels all but the most peripheral corpuscles have velocities close to the maximum and there is little difference between maximum and mean at any time (plug profile). In small vessels the flow is almost parabolic and the maximum central stream velocity is twice the mean. Both plug and parabolic profiles are examples of symmetrical laminar flow.

Where flow is known to be laminar and the exact profile is known, mean velocity may be calculated by sampling a small volume in the central stream velocity, but in the neonate it is usually necessary to have the Doppler sample volume spread as evenly as possible across the whole vessel diameter and to interpret the resultant complex Doppler signal.

Once a good signal has been obtained from a known point, further processing is needed before it can be displayed and interpreted. Either a frequency envelope can be extracted from the signal, or spectral analysis can be performed. Envelope detectors can extract instantaneous mean, maximum or root mean square frequency (zero crossing rate) of the signal; the latter is particularly prone to error. Spectral analysis is usually the preferred method of processing Doppler signals; it splits the composite signal into its component frequencies and analyses the power at each frequency to give a frequency power spectrum known as a sonogram; this is usually performed digitally using a Fast Fourier algorithm. Display of the sonogram usually places Doppler shift frequency on the y axis, time on the x axis with power represented in 3-D on a grey scale (see Figure 6). A maximum frequency envelope may be derived by tracing the outline of the sonogram either

automatically or by hand; the mean frequency envelope may also be calculated but problems similar to those in the mean frequency follower are encountered.

Options for interpretation of the processed signal include waveform analysis, velocity measurement and flow measurement.

I.IV.II. Waveform analysis techniques

These aim to correlate changes in the shape of the velocity waveform with different physiological and pathological states. They are independent of the angle of insonation and easily calculated. The pulsatility index has been most widely used. This is calculated from the formula

$$PI = \frac{S-D}{S}$$

(see Figure 4) as adapted from Pourcelot's index of resistance (Pourcelot 1975) by Bada et al(1979).

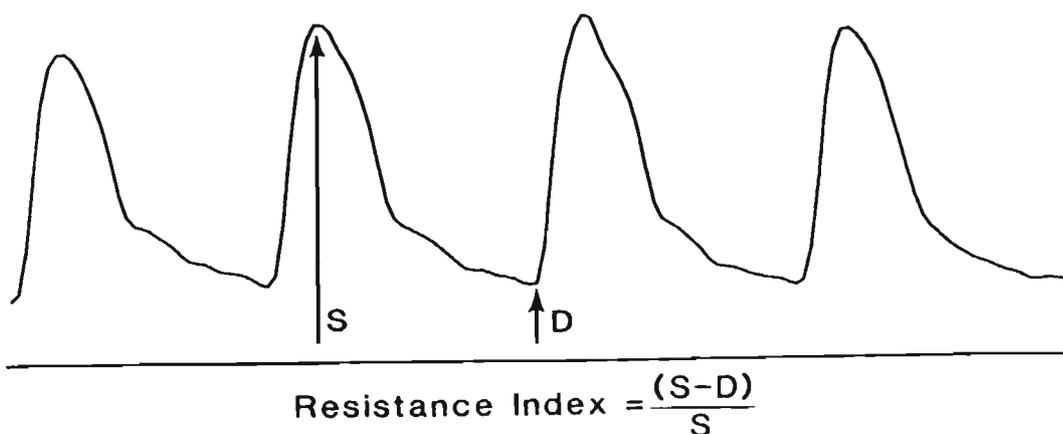


Figure 4 Pourcelot's index of resistance

PI correlates with changes in vascular resistance distal to the recording site, but is influenced by many other factors. There was a poor inverse relationship between PI and CBF using the better validated $^{133}\text{Xenon}$ clearance method (Greisen et al 1984), and failure to demonstrate an inverse relationship

between PI of the anterior cerebral artery Doppler waveform and CBF measured by the microsphere technique (Hansen et al 1983).

Principal component analysis is a pattern recognition technique (Evans et al 1985) which is more sensitive in characterising changes in the shape of neonatal cerebral Doppler waveforms. However, the physiological significance of differences in principal component analysis is unknown and this method, like PI, is also likely to be influenced by cardiac changes.

I.IV.III. Velocity measurements

Use of duplex Doppler ultrasound allows accurate vessel sampling and reproducible angles of insonation so mean cerebral blood velocity is relatively easy to obtain. Provided that the diameter of the vessel being studied does not significantly alter, mean velocity can be used to measure proportional changes in blood flow. It may not always be possible to assume that the vessel cross-section is constant (Drayton et al 1987). Mean velocity may be obtained directly from the average of mean frequency/time or, if flow is unidirectional and velocity profiles fully established, may be calculated from half the average of maximum frequency/time (Evans 1985b). The maximum frequency envelope of the Doppler arterial signal (maximum frequency/time waveform) is less susceptible to extraneous noise than the instantaneous mean frequency waveform and is usually employed for waveform analysis. Area under the velocity curve is frequently used to express velocity; depending on which form of processing is employed, AUTVC may represent the temporal average of the mean, root mean square or maximum shift.

I.V. Volumetric flow measurement - validation of the pulsed Doppler technique

The limits of ultrasound resolution do not allow accurate measurement of the diameter of neonatal cerebral arteries. Since volumetric flow equals mean velocity times cross-sectional area of the vessel, absolute blood flow is impossible to determine from Doppler studies. However, good correlation has been shown between CBFV and total CBF measured using other methods. In much of the following discussion the basic assumption is made that CBFV grossly correlates with CBF and therefore with O_2 and substrate supply as well.

As early as 1984, Lundell et al performed an in vitro validation of the pulsed Doppler technique; this allowed recordings with a well-defined longitudinal sampling volume at a specific depth under the transducer so was felt to be a more accurate technique than continuous wave Doppler for repeated measurements of blood flow velocities in deeply lying vessels. A pulsatile flow model was built which was designed to simulate small, deeply lying arterial vessels. The diameters of the model vessels, the depth under the transducers and pulsatile flow patterns were chosen to simulate conditions which can be expected when CBFV is measured with this technique through the anterior fontanelle in newborn infants.

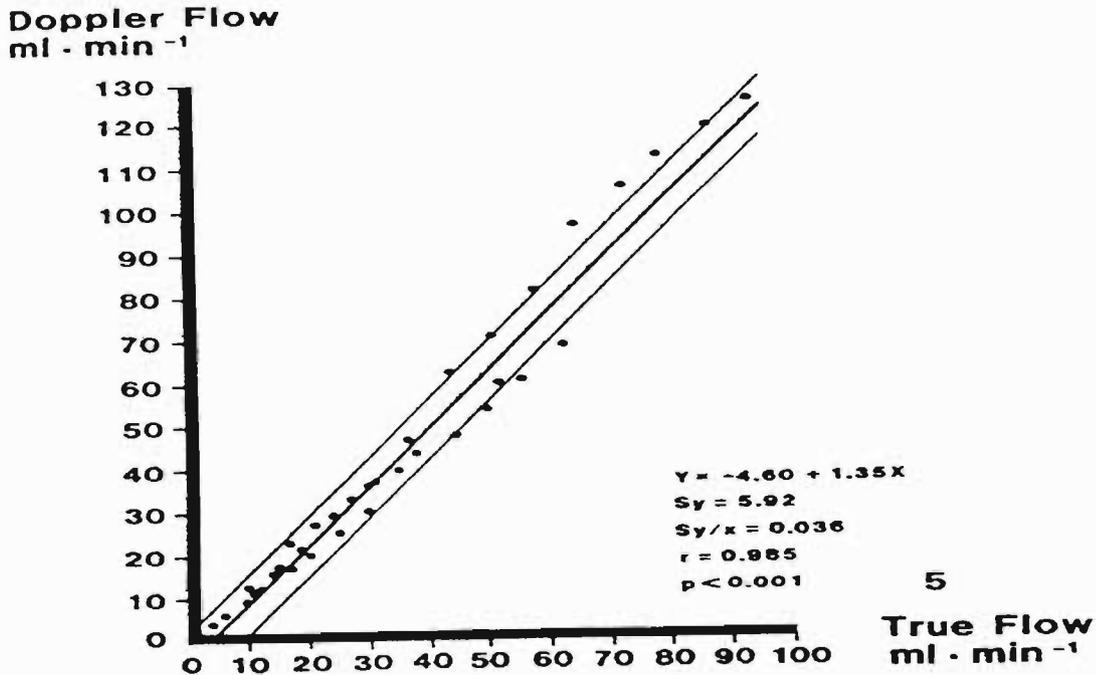


Figure 5 Doppler measured flow versus true flow in artificial blood vessels. Linear regression line and 1 SD of the measured flow(Lundell et al 1984)

Doppler recordings obtained from the simulated arterial flow model were similar to in vivo recordings of intracranial flow velocity in newborn infants. The closest linear correlation between true flow and the measured Doppler variables was recorded for the time-integrated estimated space average velocity curve. When all data from the different flows and tubing diameters were analysed together the calculated flow(distance x cross-sectional area) versus true flow gave $r=0.985$, $p<0.001$.(Figure 5.)

In 1983 Hansen et al performed an in vivo correlation between brain blood flow as measured by the microsphere method, and Doppler flow velocity measurements of the cerebral arteries via an artificial fontanelle in young piglets. The relationship between peak systolic velocity and total brain

blood flow was found to be nonlinear, with a correlation coefficient $r=0.76$, $p<0.001$. Peak systolic velocity correlated linearly with total CBF at lower values, but as total CBF increased, peak systolic velocity appeared to plateau. The same relationship was found between end-diastolic velocity and total brain blood flow (correlation coefficient $r=0.72$, $p<0.001$). Correlation between the area under the velocity curve per minute and total brain blood flow at PCO_2 values 30-50mmHg was $r=0.86$, $p<0.001$. Since the microsphere technique is considered by many to be the gold standard, this study was important in validating the usefulness of Doppler ultrasound.

Bishop et al (1986) compared transcranial Doppler ultrasound measurement of middle cerebral artery blood flow velocity with CBF using $^{133}\text{Xenon}$ clearance in 17 symptomatic patients with cerebrovascular disease. There was a wide range of hemispheric CBF (24.2ml/100gm/minute to 49.8ml/100gm/minute), and of resting middle cerebral artery peak velocity (36cm/sec to 140cm/sec). When resting CBF was compared with resting MCA velocity, correlation was poor. Response to hypercapnia of both CBF and MCA peak velocity was expressed as a reactivity index (RI) in order to relate increase in flow to an increase in end-tidal CO_2 . MCA velocity reactivity (0-21.4) and CBF reactivity (0.3-6.6) had excellent correlation ($r=0.849$) and this was highly significant ($p<0.001$).

In 1990, Rennie et al compared changes in regional blood flow measured by hydrogen clearance, with those seen in Doppler ultrasound measurement of CBFV in a related artery, after alteration in CO_2 tension in newborn piglets. The rCBF and CBFV

were related to each other but with wide 95% confidence intervals. This poor relationship may be partly explained by piglets less than 24 hours old having a pressure-passive cerebral circulation in which changes in CBFV relate more to the systemic BP than to regional changes in CBF.

Haaland et al (1994) performed simultaneous measurements of cerebral circulation with electromagnetic flowmetry and Doppler ultrasound velocity in 9 newborn piglets. Electromagnetic flowmetry is an established method in measuring continuous blood flow. An essential question when validating CBFV measurements obtained with a constant angle of insonication, is whether the diameter of the vessel under investigation changes during the study. Flow was calculated using an electromagnetic probe fitting closely around the common carotid artery of each piglet. Such a probe induces an electromagnetic field through the vessel, and the voltage generated when blood as a conductor cuts through the magnetic field, is proportional to the volume flow.

Each animal was subjected to CO₂ inhalation, haemorrhage, hyperventilation and blood transfusion. The interventions were randomly performed to avoid time-dependent results. Simultaneous recordings (n=142) with Doppler ultrasound and EM flowmetry in different flow situations were obtained, with the average mean arterial blood pressure changing from 28 to 70mmHg, and the average PaCO₂ varying from 22.5 to 55.5mmHg. Changes in EM flowmetry and estimated Doppler flow when MABP was varied between 28 and 70mmHg, followed each other closely. The changes in CBFV from an intracerebral artery also closely followed the EM flow in response to CO₂ breathing and

hyperventilation. The correlation EM/Doppler with either both transducers on the modified common carotid artery or with the Doppler probe on an intracerebral artery was unaffected by changes in MABP or PaCO₂. There was a linear relationship between common carotid EM flow and estimated Doppler flow (either common carotid or intracerebral) for each individual, for the two sets of recordings. There were substantial differences in the slopes of the lines, showing that the diameter of the common carotid artery was not constant between animals as was assumed in the calculations. The differences in the slopes does not affect the ability of Doppler ultrasound to predict relative changes in CBF in individual subjects.

The extent to which CBFV correlates with CBF during changes in systemic BP, was addressed by Newell et al(1994). Electromagnetic flow measurements were compared with TCD measurements of the ipsilateral MCA during surgery of the carotid artery. Spontaneous fluctuations of systemic BP and artificially induced hypotension led to similar results in CBF and CBFV, further validating Doppler ultrasound measurements. In adults, Giller et al(1993) have also shown correlation between TCD and an operating microscope, of the reactions of intra-operative vessels to changes in MABP and end-tidal CO₂.

I.VI. Neonatal intracranial Doppler measurements

In the newborn, especially when premature, the anterior and middle cerebral arteries are freely accessible through the open anterior fontanelle and the temporal bones. Thin bone and tissue allow good imaging and clear Doppler signals. The ACA has been most commonly used in Doppler studies. Archer et al(1985) demonstrated the 2 optimal sites to obtain the

greatest Doppler shift from the ACA in the newborn via the AF. Using this approach, the angle of incidence is not greatly different from zero degrees (see Figure 6).

With duplex Doppler scanning therefore, the insonating angle can be kept constant. It is occasionally possible to differentiate signals from right and left sides but most systems do not have adequate resolution to do this reliably.

In newborn infants, Greisen et al (1984) compared CBFV measured by Doppler ultrasound, with CBF measured by $^{133}\text{Xenon}$ clearance (Table 6).



Figure 6 Colour Doppler identification of the anterior cerebral artery

Table 6. Doppler ultrasound measurements of pulsatility index, mean flow velocity and EDFV, and correlation to CBF-Xe (Greisen et al 1984)

	PI	MFV (cm/sec)	EDFV (cm/sec)
Anterior cerebral artery			
Continuous wave	0.56±0.09 r=-0.41 (-0.54)	8.8±3.7 r=0.49 (0.64)	6.0±3.0 r=0.58 (0.80)
Range-gated	0.72±0.09 r=0.59 (-0.71)	10.5±4.0 r=0.69 (0.77)	10.8±6.0 r=0.65 (0.74)
Internal carotid artery			
Continuous wave	0.62±0.09 r=-0.47 (-0.58)	7.7±3.0 r=0.62 (0.82)	5.1±2.8 r=0.65 (0.84)
Range-gated	0.77±0.07 r=-0.56 (-0.65)	10.0±3.7 r=0.75 (0.83)	9.5±4.6 r=0.82 (0.86)

All Doppler ultrasound variables measured ie PI, mean flow velocity cm/sec and EDFV correlated significantly with the result obtained by ^{133}Xe clearance, but there were significant differences in the correlation coefficients. The range-gated Doppler ultrasound technique gave more accurate and precise results than did continuous-wave techniques.

The internal diameter of the ACA is approximately 1mm (Seydel 1965); cross-sectional area(CSA) is therefore small relative to the sample size so even insonation should not be a problem. As mentioned above however, the small vessel size makes volume measurement impossible.

I.VII. Intracerebral autoregulation in the VLBW infant

In order to achieve cerebral autoregulation CBF must be maintained independent of systemic BP, and must also be capable of adapting to a variety of changing metabolic requirements in the brain. The basis for this adaptation is ongoing change in the arteriolar vascular bed in response to different factors including neurological, biochemical, pharmacological and humoral stimuli.

Many explain autoregulation as a myogenic response to stimuli under the control of a vasomotor centre. However, neither the whereabouts of this centre, nor the biochemical and physiological control of this regulation has been adequately clarified(Ipsiroglu et al 1999). Luciano et al(2000) propose that CBF is regulated by 2 control mechanisms, one dynamic and one metabolic. The dynamic element includes maintenance of MAP, circulating blood volume, cardiac output and haematocrit, while the metabolic component regulates blood gas components, glucose and temperature.

Cerebral perfusion pressure is the difference between MABP and central venous pressure(CVP). Because of the thin vessel wall, CVP approximates intracranial pressure(ICP) so $CPP = MABP - ICP$. At a constant blood pressure, a continuous rise in ICP leads to a fall in CPP.

In the normal brain, CBF is maintained constant over a wide range of cerebral perfusion pressures in order to provide adequate oxygen and substrates to preserve neuronal integrity. To maintain stable flow, vascular resistance must increase with systemic hypertension and decrease with systemic hypotension. This is achieved by arteriolar vasoconstriction and dilatation respectively(Harper et al 1966).

Because of its non-invasive properties and ease of use, Doppler ultrasound has been the main method employed to investigate cerebral autoregulation in the preterm human infant. Using flow velocity measurements, CPP may be evaluated even though flow volume cannot be quantified because of technical limitations(ie vessel CSA). Although an abnormal flow pattern implies abnormal ICP, the reverse may not be true. Poiseuille's law for steady laminar flow in long cylindrical tubes states that $CBF = CPP/CVR$. Autoregulation implies that when CPP changes, CBF is maintained by a change in CVR. However, both $PaCO_2$ and the volume compliance of the vascular bed may independently affect CVR, so arterial BP may not be directly proportional to CBF; flow ceases at the critical closing pressure(CCP) rather than at zero(Burton 1951). The concept of a CCP postulates that there will be no forward CBF whilst MABP is less than CCP.

I.VII.I. Vessels involved in intracerebral autoregulation

Traditionally, small distal arterioles were thought to regulate cerebrovascular resistance. Now there is good evidence that the major cerebral arteries play an important role. Heistad et al(1978) using the microsphere technique in dogs, demonstrated that both large cerebral arteries and arterioles play an active part in regulation of CBF during changes in arterial blood gases and CPP. Kontos et al(1978) observed the pial circulation of parietal cortex in cats using cranial windows, and demonstrated that the larger surface cerebral vessels from the circle of Willis to pial arteries 200um in diameter were responsible for adjusting blood flow over a wide range of arterial BP's. Further work by the same group(Kontos 1989) described changes in the cross-sectional area of large vessels, as much as a 5% change under steady state conditions, and a change of 10% with a fall in blood pressure. The degree to which fluctuations in BP in the preterm newborn can cause changes in the cross-sectional area of large vessels has not been examined. This study is often quoted by critics of the Doppler method of assessing blood flow.

I.VII.II. Range over which autoregulation is effective

Cerebral autoregulation is maintained only within a certain range of CPP; outside this, flow is pressure passive. The range varies with different species and different age groups.

Ahman et al(1983) claimed that autoregulation is intact if CBFV remains constant when blood pressure fluctuates by 5% or less. Jorch and Jorch(1987) used Doppler to measure CBFV of

the right internal carotid artery in 23 neonates and found a positive correlation between the mean arterial BP and time-averaged maximum blood velocity in 16 of these. Features of this group included gestation less than 31wk, BWT less than 1501 grams and mean carotid blood velocity less than 20cm/sec. Jorch et al assumed that these babies lacked cerebral autoregulation because their brain perfusion lay below the lower limits of "the range of autoregulation".

In the unsedated infant lamb, Arnold et al (1991) studied global brain blood flow, and found that this remains constant for a range of mean aortic blood pressure from 38% below to 12% above the normal mean. Study in the preterm fetal lamb (Papile et al 1985) found autoregulation of CBF to exist in the fetus, but over a narrower range than in the term lamb (approximately 80%), and showed that the fetal resting mean carotid arterial BP lies closer to the lower limit of autoregulation than at term.

Recently, continuous transcranial Doppler (TCD) has been used to further explore autoregulation in the preterm infant. Infants less than 33 weeks gestation were classified as having intact autoregulation if CBFV normalised earlier than BP (within 2 seconds), whereas in those assessed as lacking autoregulation, this process was delayed (Panerai et al 1995). The same group found that control term infants demonstrated an initial brief period when CBFV followed MABP, but this quickly returned to baseline. In 13 high risk infants autoregulatory responses were impaired, such that CBFV closely mirrored MABP. Preterm controls also failed to show intact cerebral autoregulation (Boylan et al 2000).

Another group (Kohler 1997) studying autoregulatory capacity longitudinally in healthy newborns, found the tilting test to be complete only at 4-6 weeks of age. They concluded that the ability to retain baseline CBFV within a given time after tilting, rather than the slope of reaction pattern, indicated the proficiency of autoregulation.

I.VII.III. Regional regulation of cerebral blood flow

Alteration in the metabolic rate of a region is somehow matched by an alteration in flow; examples of this are seizures, where flow and metabolic rate are both increased, and coma, where both are decreased. This form of regulation allows CBF to adapt to regionally defined metabolic needs. Local CBF varies with local O_2 and glucose consumption. Thus local vasodilators cause arteriolar vessels to dilate. Lassen et al (1978) showed that CBF varied in different parts of the human cortex, reflecting changes in activity of those areas. Work by Laptook et al (1983) and by Ashwal et al (1981) supported this finding. As described above, this mechanism is regulated by changes in arteriolar diameter which alter CVR. An increase in brain activity is matched by an increase in CBFV (Aaslid 1987, Droste et al 1989). Important in this process are such vasoactive substances as hydrogen ions, potassium, adenosine, prostaglandins, calcium and osmolarity. A well-known example is the vasodilatation caused by increased hydrogen ions during metabolic acidosis (Paulson et al 1990).

The concept of metabolic regulation also applies to changes with substrate supply, since these relate to behavioural states and body temperature. Doppler flow has been

used to study changes with glucose, oxygen, sleep and body temperature.

I.VIII. Use of Doppler waveform measurements during physiological changes in the newborn infant

A constant cross-sectional area has been demonstrated in insonated proximal vessels in adults, but direct investigation of the CSA has not been performed in the newborn. However, various studies show correlations similar to those seen in adults (Archer et al 1986, van Bel et al 1988, Levene et al 1988).

The PaCO_2 level is one of the principle mediators of CBF. In the range of normocapnia (25-50mmHg), there is an almost linear relationship between CBFV and PaCO_2 . Above and below these values the Doppler curve becomes asymptotic (Ringelstein et al 1988). During hypercapnia in the adult, an increase of around 25% was seen per kPa (Hauge et al 1980, Markwalder et al 1984). Infants, especially when preterm, have a narrower range over which autoregulation operates.

Wyatt et al (1991) used NIRS to study cerebral blood volume in 17 ventilated newborn infants (gestation 26-41 weeks, median 29 weeks). Change in CBV per kPa change in arterial CO_2 tension was measured within the range 3.9-9.6 kPa. There was a highly significant linear increase from $0.07\text{ml}\cdot 100\text{g}^{-1}\cdot \text{kPa}^{-1}$ at 26 weeks gestation to $0.51\text{ml}\cdot 100\text{g}^{-1}\cdot \text{kPa}^{-1}$ at 40 weeks. This is supported by the findings of Levene et al (1988) who studied CO_2 reactivity in 19 mechanically ventilated infants of 33 weeks gestation or less; there was a 44% (median value) rise in CBFV per kPa rise in PaCO_2 in 21 infants tested within the first 24 hours of life.

This increased to a 53% (median value) rise in 20 infants tested 24 hours or more after birth.

Haaland et al (1995) studied CBFV during changes in MABP induced by haemorrhage, or changes in PaCO_2 in 56 anaesthetised ventilated piglets 0-26 days old. As in Wyatt's study, the CO_2 reactivity increased with age, from $6.5\% \text{kPa}^{-1}$ on day 1 to adult levels of $25\% \text{kPa}^{-1}$ for piglets older than 4 days.

To validate CBFV data, both electromagnetic flow and precerebral Doppler ultrasound velocity were recorded from the same common carotid artery with the extracranial branches tied off. There were no differences between the results using these 2 methods, nor between these results and those obtained when CBFV was recorded from an intracerebral artery, and the electromagnetic flowmeter recorded from the carotid artery. The vessel diameter appeared stable during these interventions.

Severe hypoxia however, especially if prolonged, may alter the influence of PaCO_2 on CBF. Menke et al (1993) found that in preterm infants less than 33 weeks gestation, the direct effect of PaCO_2 on CBFV was ten times greater than the effect of PaO_2 . van Bel et al (1988) studied infants at less than 34 weeks gestation and found that there was a significantly greater increase in peak systolic flow velocity during hypercarbia with hypoxia than was seen during hypercarbia with normoxia.

Pryds et al (1990) studied 18 spontaneously breathing preterm infants (GA 27-33 weeks, mean 30.3 weeks) being treated with nasal continuous positive airway pressure. CBF was measured at 2 hours and at 3 hours after birth using the intravenous $^{133}\text{Xenon}$ clearance technique; simultaneous arterial

BP, blood gases and blood sugar were measured, since low blood sugar is known to have a pronounced effect on the CBF (Pryds et al 1988). In that study, CBF increased by a mean of 29% per kPa increase in arterial CO₂ tension and this estimate was not altered after introduction of changes in MABP and/or transcutaneous arterial PO₂ in the regression analysis.

They concluded that preterm infants have the same capability as adults with regard to pressure-flow autoregulation of CBF unless insults leading to vasoparalysis have occurred.

I.IX. Clinical studies employing CBFV measurements

Many clinical studies have been performed using cerebral Doppler ultrasound to study CBF changes which occur during circumstances and events early in life in the human neonate. Such situations include patency of the ductus arteriosus, perinatal asphyxia, brain injury and brain death, posthaemorrhagic hydrocephalus and administration of various drugs.

I.IX.I. Patent ductus arteriosus

The ductus arteriosus is patent in the fetus. In most normal term infants, this closes functionally soon after birth as pulmonary blood flow changes from a low flow, high pressure system to a high flow, low pressure system. The PDA then closes structurally over several weeks. In the VLBW infant, the ductus often remains patent but it now seems that prematurity per se, down to a gestation of 28 weeks, does not result in prolonged ductal patency; rather, respiratory failure and other morbidity seem important in the aetiology (Skinner et al 2000). A large left-to-right shunt through the PDA can lead

to heart failure, decreased lung compliance and decreased tissue perfusion and is known to increase likelihood of chronic lung disease.

Currently, diagnosing a PDA includes clinical examination plus imaging the duct with cross-sectional and colour Doppler echocardiography. Colour Doppler makes localisation and visualisation of the PDA much easier, and a significant PDA can sometimes be diagnosed by pulsed Doppler echocardiography days before clinical signs appear. Prior to the advent of colour Doppler, diastolic ductal flow into the main pulmonary artery was considered diagnostic of PDA (Stevenson et al 1980). Also, disturbed CBFV in the ACA with absent or retrograde diastolic perfusion as estimated by Doppler sonography showed 100% sensitivity and specificity for diagnosis of PDA (Kupferschmid et al 1988).

Couser et al (1996) reported an incidence of PDA of 86% in 90 infants with birthweights 600-1250grams on day 1 of life. The Vermont Oxford database reported an incidence of 31% in VLBW infants but the timing of diagnosis is not stated (1993). The incidence appears to be highest in the first hours of life in the sickest infants; Shortland et al (1990) found a PDA in 70% of 120 VLBW infants in the first week of life. In 1981 Perlman et al studied 55 preterm infants (BWT less than 2kg). Ten developed PDA between days 3 and 10 of life. Cerebral Doppler ultrasound was performed using the ACA and the mean PI value prior to the diagnosis of PDA was 0.67, SD \pm 0.05. At the time of diagnosis, the PI had risen in every patient (mean 0.91, SD \pm 0.03). After ductal closure the mean was 0.66, SD \pm

0.03. Both increases and decreases were statistically significant ($p < 0.001$). The constant determinant of changes in the PI was a change in the diastolic flow velocity, whereas changes in the systolic flow velocity were variable. The temporal relationship of the changes to the development of intracranial haemorrhage was not consistent, so Perlman did not believe that the rise in PI was due to haemorrhage.

Wright et al (1988) studied 10 normal newborn infants and found that ductal closure was associated with a significant rise in mean arterial BP ($p < 0.05$), and a significant decrease in pulsatility in the carotid, anterior cerebral and middle cerebral arteries. They believed that the temporal association between ductal closure and decreased pulsatility suggested that CBFV patterns reflect ductal shunting in normal term newborns since cerebral autoregulation should compensate for a decrease in flow with vascular dilatation in such infants. The increase in PI seen with ductal shunting may be due to diastolic runoff rather than to an increase in cerebrovascular resistance.

I.IX.II. Perinatal asphyxia, brain injury and brain death

Doppler ultrasound measurements of CBFV have been used to aid prognosis after perinatal asphyxia and brain injury. In neonates, generally these have been short-term measurements to assess pathological haemodynamic conditions.

Some have found low PIs in the early phase of asphyxia in term infants reflecting a higher diastolic amplitude, whilst those with ICH/IVH had a significantly higher PI than controls (Bada et al 1979, Mires et al 1994). Archer et al (1986) claimed that two thirds of term asphyxiated newborns who had abnormal waveforms died or were handicapped. This use of

Doppler ultrasound in the diagnosis of brain injury and outcome remains contentious.

The clinical criteria for brain death also remain controversial, especially in the very young. In 32 brain-dead infants and children, Ahmann et al (1987) correlated CBFV patterns measured by Doppler ultrasound with clinical examination and where possible, radionuclide cerebral angiography. Ipsiroglu et al (1999) believe that for verification of brain death in neonates, pendular flow should be reproducible not only bilaterally to exclude unilateral haemorrhage, but also in all major vessels.

I.IX.III. Doppler studies in posthaemorrhagic hydrocephalus

The role of an increase in pulsatility index or resistance index as an indication for surgical drainage in neonatal hydrocephalus remains debatable (Goh and Minns 1995, Rennie 1997). This is mainly because open fontanelles and sutures allow for a certain amount of cerebral oedema without changing these indices.

Perhaps 24 hour monitoring of Doppler ultrasound to detect critical changes in cerebral perfusion during intracranial pressure fluctuations would help resolve the issue of when shunting should be performed (Goh et al 1992).

I.X. Autoregulation, cerebral blood flow and injury

Impaired regulation of CBF is believed to be of major importance in the aetiology of cerebral damage in preterm neonates. Such injury in the preterm newborn infant has been linked with increased CBF or hyperperfusion, decreased flow or hypoperfusion, and fluctuant flow with extremes of beat-to-beat variability.

Since arterial BP is now frequently measured continuously from an indwelling catheter in sick preterm infants, many studies have attempted to correlate BP and its fluctuations with cerebral insult and outcome.

I.X.I. Arterial hypertension

Arterial hypertension was suggested as a key factor in the aetiology of ICH by Lou and Friis-Hansen(1979). During motor activity, nursing procedures, apnoea and seizures, mean aortic BP in the neonate rose from a resting level of 30-40mm Hg to one around 80-90mm Hg; without adequate cerebral autoregulation, such a hypertensive peak would be transmitted to the capillary bed of the germinal matrix and might lead to haemorrhage. Goddard et al's animal studies(1980) supported this; germinal matrix haemorrhages were found in all 9 beagle puppies where moderate hypertension was rapidly induced. More recently, Gronlund et al(1994) also found raised arterial BP to be significantly associated with peri-intraventricular haemorrhage in preterm infants.

I.X.II. The cerebral hypoperfusion theory

Miall-Allen et al(1989) found that in babies less than 31 weeks gestation, MABP of less than 31mm Hg for an hour or more was significantly associated with severe ischaemic or haemorrhagic lesions, or death within 48 hours. No infant with MABP greater than 30mm Hg died or developed severe lesions. The results of Bada et al(1990) also support the idea of hypotension predisposing to ICH. She measured minute-to-minute MABP during the first 48 hours of life in 100 infants with BWT less than 1501gm and found that the 28 who developed grades 2-4

IVH had consistently lower mean arterial pressures than those who developed grades 0-1 IVH.

In a recent study using NIRS, Meek et al (1999) demonstrated an association between low CBF on day one of life, and the subsequent development of severe IVH in VLBW infants.

I.XI. Variability in physiological systems

Extremes of beat-to-beat variability of CBFV have also been proposed as risk factors for cerebral injury in the VLBW and ELBW infant (Bada et al 1990, van Bel et al 1987, Perlman et al 1983, 1985).

However, some variability in physiological systems has long been recognised as a normal occurrence. Such variability has been identified in observations of heart rate, blood pressure and cerebral blood flow (van Ravenswaaij-Arts et al 1990, 1994, Bada et al 1990, Miall-Allen et al 1989).

In the fetus and newborn, the autonomic nervous system plays an important part in maintaining cardiovascular well-being via a negative feedback loop, with a time lag which leads to fluctuations in HR and BP. Although these oscillations have been studied extensively, current knowledge of the interactions between the parasympathetic and sympathetic elements remains limited. In the fetus, humoral factors correlate directly with HRV but this is not true after delivery (Padbury et al 1988). The SNS appears to have a major role in the transition at birth. The tone of both PNS and SNS increases with maturation, with a gradual shift to PNS dominance. As the infant develops, nervous control of BP becomes more functional.

Spectral signal analysis is frequently applied to variability in HR, BP and CBFV.

I.XI.I. Signal analysis- fast Fourier transform and spectral analysis

The returning Doppler shifted spectrum which has insonated a blood vessel, contains much complex information. Blood flowing within the vessel is travelling at different velocities at different points within the vessel lumen, and at different times in the cardiac cycle. Fourier transform spectral analysis allows examination of the frequency components. The spectrum analyser takes in 5msec of signal, resolving the frequencies within it, and displaying the result as an array of pixels. The length of each pixel represents 5msec and the height is usually one hundredth of the total frequency range. The grey scale assigned to each pixel is a measure of the power of the frequency component of that pixel. The results are displayed as a visual sonogram.

Spectral analysis of a Doppler signal has in the past been performed using a variety of equipment but currently most instruments use the FFT method. Fast Fourier transform was first described by Cooley and Tukey(1965), and because it is so rapid, revolutionised spectral analysis using digital methods.

The best spectral resolution obtainable from a transform is given by the reciprocal of the data segment length used(eg resolution can be no better than 200Hz on a 5msec length of data). In practice the data is usually "windowed" to prevent spectral leakage. This reduces spectral resolution further.

I.XI.II. Variability of heart rate and blood pressure in neonates

The influence of respiration on heart rate and blood pressure variability was first recognised in 1733 by Stephen Hales; he found that in the horse, changes in blood pressure and pulse rate were related in a regular manner to the respiratory pattern. In 1847 Ludwig used a chymograph to show that heart rate quickened with inspiration and slowed with expiration on a regular basis. This is now known as respiratory sinus arrhythmia.

Hedman et al(1992) used anaesthetised dogs to show that the mechanism of RSA is mainly the result of central nervous control. Non-neural factors played only a small part.

In neonates, RSA is of smaller magnitude than in older babies and children. This may be the result of a higher respiratory rate, or because vagal control(PNS) is still evolving. All components of HRV are decreased in situations of compromise such as RDS or severe brain damage(Aarimaa et al 1988, van Ravenswaaij-Arts et al 1991).

In term infants, three spectral regions of HR variability have been identified - very low frequency at $<0.02\text{Hz}$, low frequency at $0.02\text{-}0.2\text{Hz}$ and high frequency at $>0.2\text{Hz}$. In contrast to adults and older children where respiration and HRV are strongly related through high frequency RSA, in the first week of life in term infants, respiration and HRV were related through breath amplitude sinus arrhythmia ie the low frequency region of the spectrum, rather than on a breath-by-breath basis(Dykes et al 1986); they proposed that this may relate to the more rapid respiratory rate of newborn infants where the

parasympathetic nervous system is relatively immature, and the sympathetic nervous system is dominant. van Ravenswaaij-Arts et al(1994) found an increase in low frequency HRV with increasing GA, while HFV increased during early postnatal life.

Other workers(Japundzic et al 1990) found that HRV in the low frequency spectrum is mediated by both PNS and SNS, whereas RSA is vagally mediated(ie PNS).

I.XI.III. Mayer waves

In the 19th century, Traube(1865) and Hering(1869) described fluctuations in blood pressure at the same frequency as respiration, in animals which were incompletely paralysed, once artificial respiration was discontinued(Traube-Hering waves).

In 1874 Mayer reported a periodic waxing and waning of BP with a much longer time course than that of normal respiration in animals with spontaneous respiratory movements, and Guyton in 1951 reported cycles of BP at a frequency 1-5 cycles per minute in deteriorating animal preparations.

Although it has long been postulated that Mayer waves reflect rhythmic changes in medullary vasomotor function, opinions differ about the factors causing this rhythmicity.

Using an artificial heart to eliminate rhythmical periodicities such as altering heart rate and cardiac function, Yambe et al(1993) found results to suggest that Mayer waves originated at least in part from peripheral vascular resistance. These fluctuations in the circulatory system influence the arterial baroreflex system and transfer to the sympathetic outflow through the central baroreflex system. This suggests that rhythmical fluctuations in the

cardiovascular system originate at least in part from these vascular periodicities (Kaminski et al 1970).

I.XII. Cerebral blood flow velocity variability

In the last 25 years, two other frequencies of natural oscillations have been recognised in BP as well as in HR using spectral analysis; a peak around 0.05Hz is thought to be related to fluctuations in peripheral vascular tone associated with thermoregulation, and another around 0.12Hz to be related to the frequency response of the baroreceptor reflex (Hyndman et al 1971, Kitney 1975).

Although autonomic reflexes and sympathetic activity are important regulators of BP and other cardiovascular functions in the fetus and newborn, hormonal influences on these reflexes differ significantly early in development compared with their effect in adults. Endogenous angiotensin II is very important in the resetting of arterial baroreflexes early in life, while vasopressin, even in very high circulating levels, has little effect until adulthood (Segar et al 1997).

Jahnukainen et al (1993) demonstrated significant differences in vasomotor thermoregulation even between normal term and preterm babies, suggesting that vasomotor control is immature in the preterm infant. The same group found cardiovascular responsiveness to periodic thermal stimulation inferior in both preterm and IUGR infants in the first 2 months of life (Jahnukainen et al 1996).

I.XII.I. Use of spectral analysis in the assessment of CBFV

Interactions between respiration and BP have now been studied with regard to fluctuations in CBFV. These fluctuations have been demonstrated by examination of CBFV

traces both visually (Rennie et al 1989), and using spectral analysis (Bignall et al 1988); spectral analysis of waveforms was used to quantify respiratory-induced cardiovascular variability in 22/38 recordings in 16 ventilated VLBW infants. One frequency component (0.5-1.5 Hz) was found at the respiratory rate, another at the heart rate (1.5-3 Hz), and a third at very low frequency (0.01-0.15), which was attributed to thermoregulation and baroreceptor modulation. They proposed that transmission of respiratory variation to CBFV is common in sick, ventilated VLBW infants.

Anthony et al (1991) also described slow variations of CBFV in newborn babies at a frequency of 1-5 cycles per minute (0.02-0.08 Hz).

I.XII.II. Flow studies using Doppler ultrasound in the assessment of cerebral blood flow velocity variability

Doppler flow studies of cerebral vessels form the basis of support for or against the theory that extremes of beat-to-beat variability of cerebral blood flow velocity are risk factors for intracerebral injury. Doppler is a non-invasive technique which measures CBF velocity - a derived value which estimates perfusion, but not volumetric flow. It does however depend on the assumptions that vessel size remains constant and that there is no intracranial redistribution of flow. Many studies employing CBFV as measured by Doppler, calculate the area under the peak frequency envelope for each of 10-20 cardiac cycles and express the result as the coefficient of variation where CV equals standard deviation/mean expressed as a percentage.

Extreme variability in CBFV as a risk factor for intracerebral injury remains controversial. Bada et al (1990),

showed that the 28/100 VLBW babies who developed IVH spent a greater percentage of the study time with a coefficient of variation of MAP either greater than 12% or less than 3%, than did their matched controls. She concluded that SOME but not marked variability in MAP signifies healthy physiology.

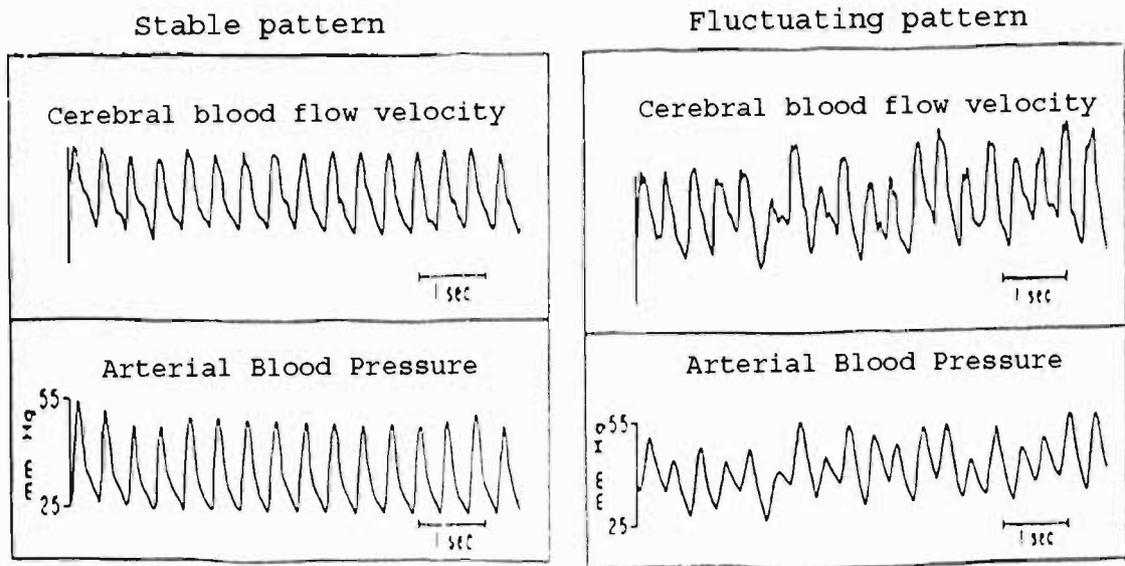


Figure 7
Stable and fluctuating patterns of CBFV and
simultaneously recorded arterial BP

Perlman et al (1983) measured beat-to-beat variability of both MAP and CBFV simultaneously in 50 VLBW babies who were ventilated for RDS. The BP pattern was directly reflected in CBFV and was designated either stable (CV% 7-11%) or fluctuating (CV% 17-31%). Of the 23 with a fluctuating pattern, 21 developed IVH in the subsequent 24 hours; of the 27 with a stable pattern only 7 developed IVH. Figure 7 demonstrates the 2 different patterns. This group next (1985) randomly assigned a further 24 VLBW babies being ventilated for RDS to either a control or a treatment group; muscle paralysis was

instituted in the latter. Intraventricular haemorrhage developed in 10/10 of controls but only 5/14 of the treatment group and 4 of these 5 haemorrhages occurred after paralysis was discontinued. They concluded that paralysis reduced the incidence of IVH by converting the pattern of CBFV from fluctuating to stable.

And finally, in a prospective study of 55 babies weighing 500-2670 grams (25-33wk gestation), van Bel et al (1987) found a striking relationship between a fluctuating CBFV pattern and the subsequent onset of PVH. A CV% of 11.2% or less was considered stable.

Others dispute that highly variable CBFV is a risk factor for intracerebral injury. Miall-Allen et al (1989) studied 22 babies less than 32 weeks gestation who were ventilated for a minimum of 12 hours for RDS. She measured the CV% of the systemic MAP each minute from 6-36 hr of age; BP fluctuation was greater for a longer proportion of the measured time in those who did not develop IVH (n=12) than for those who did (n=10). Values for CV% were in the same range as those found by Rennie et al (1987) ie a maximum of 15%, not as high as the 30% reported by Perlman et al (1983). Ten of 22 babies were paralysed, with approximately equal numbers in each group, but their results did not support the claim that paralysis reduces the incidence of IVH.

Colditz et al (1989) found that sedation and paralysis both reduced CBFV variability but that the group with lower variability had a higher incidence of IVH so concluded that CBFV was not important in the aetiology of haemorrhage. No

baby in that study, however, had a CV% of CBFV greater than 10%.

I.XII.III. Other influences on cerebral blood flow velocity variability

Rennie et al(1987) found that CBFV was significantly lower in ventilated low birthweight babies on day 1 of life when synchronous ventilation was achieved (median CV% 5%), than where asynchrony prevailed (median CV% 11%). In a later study Rennie(1989) showed that infusion of plasma and/or dopamine significantly reduced variability of CBFV from a median CV% of 13% to one of 4-5%, and proposed that marked variability may indicate low circulating volume.

Indomethacin, a prostaglandin synthesis inhibitor, is currently used for medical closure of patent ductus in premature infants. It has been shown to lead to a significant decrease in CBFV when given rapidly by intravenous administration (Cowan 1986, Evans 1987). More recently, CBFV was studied following continuous infusion of indomethacin over 36 hours in 9 premature infants (Hammerman et al 1995). In contrast to the decreased velocity observed after rapid injection, slow continuous infusion showed no significant change in flow velocities.

Other drugs which have been shown to affect CBFV include aminophylline which Chang(1994) found to decrease velocities in both middle and anterior cerebral arteries in 10 infants. Although CO₂ levels were also significantly decreased 2 hours after the dose, he claimed that the reduction in CBFV was more than could be accounted for by the lower CO₂ levels alone. Caffeine, however, was not associated with significant changes

in CBFV in 7 clinically stable preterm infants with apnoea (Saliba 1989).

In conclusion, cerebral injury appears to be dependent on cerebral blood flow disturbance. Most authors support the theory that cerebral autoregulation is absent or incomplete in many preterm infants and so any variability in systemic arterial blood pressure may be transmitted to cerebral flow. This may be detrimental. However, variability in CBFV at the respiratory frequency may not relate to lack of cerebral autoregulation, but rather be a normal phenomenon under the control of a central mechanism, the same as or similar to that regulating heart rate variability. Certainly, absence of ANY variability in heart rate is an adverse prognostic indicator for RDS (Jenkins et al 1980).

This study attempted to clarify some of the questions surrounding variability in CBFV.

Chapter II. Methods

II.I. Patients

A consecutive cohort of babies of birthweight less than 1501 grams, including multiple births, admitted to the Special Care Baby Unit at the Rosie Maternity Hospital in Cambridge between December 1989 and October 1990 were eligible for this study; those with functioning indwelling arterial catheters are included in all analyses. Although multiple births may have a higher incidence of neurological damage, they were not excluded since the study aimed to examine the role of variability in CBFV related to respiration and also to morbidity, rather than the cause of the variability.

Of the total number of babies, those who remained longer than 4 weeks were the subjects of a longterm study. Infants weighing less than 1501 grams at birth were excluded if they had a lethal congenital malformation, were admitted to the unit after twenty-four hours of age or were less than the third centile for weight for gestational age; studies in babies (Kempley et al 1991), and in animals (Bauer et al 1989) have shown altered responses in cerebral flow in the presence of IUGR.

Informed consent was obtained from one or both parents. The study was approved by the District Ethical Committee.

II.II. Study Design

This study encompassed both acute and longterm phases.

Variability in CBFV encompasses both beat-to-beat variability and also fluctuations at much lower frequencies. Most investigators in this field believe that it is the extreme variability in beat-to-beat fluctuations which may be a risk

factor for neurological morbidity (Bada et al 1990, van Bel 1987, Perlman 1983, 1985).

II.II.I. Acute Phase

This study aimed to examine short-term variability in CBFV in a cohort study of preterm, VLBW infants, to clarify whether this variability was universal, or whether its presence selected out at-risk infants.

Because fluctuations in arterial BP have been linked to the respiratory frequency in infants, I aimed to examine systematically, in this cohort of VLBW infants, the appearance of a respiratory signal in blood pressure and CBFV variability, and to explore which factors were important in determining the presence or absence of the respiratory frequency in CBFV. Since previous work (Wright et al 1988, Perlman et al 1981) suggested that a moderate or large PDA has an effect on CBFV, this was also investigated.

Also, because many believe that cerebral autoregulation is absent or impaired in sick VLBW infants, I wished to examine how frequently variability in arterial blood pressure is directly reflected in the cerebral circulation.

Most infants in the study initially required ventilation for respiratory support, and the insertion of an indwelling arterial line (either peripheral or umbilical), both for the purpose of monitoring arterial blood gases, and for accurate and continuous recording of blood pressure. This group of babies had recordings made of CBFV, arterial blood pressure, ventilator pressure and spontaneous respiratory patterns generated, commencing in the first 24 hours, then on days two, three and seven of life (and weekly thereafter whilst invasive blood

pressure monitoring and/or artificial ventilation continued). Although it was impossible to standardise the timing of recordings because of practical clinical management issues, each study was performed whilst the infant was as stable as possible, never during periods of intervention.

These studies consisted of 4-channel recordings, and lasted almost one minute (53 seconds) on each occasion. The duration of the study was restricted to 53 seconds by technical limitations of the ultrasound machine and microcomputer-based system used to process the Doppler signal. Recordings of all four physiological parameters were simultaneous, to allow synchronisation of the analysis. Usually, at least 2 recordings were made in the same session within 1-2 minutes of each other, and the recording which was technically best was used for analysis. No parameters altered during any session. A recording was considered good technically if there was minimal loss of Doppler signals from the anterior cerebral artery; where loss of signal occurred, the usual reason was movement on the part of baby or recorder.

Examples of the 4 channels of raw data are shown in Figures 8 and 9. Monitoring of CBFV, respiratory parameters and invasive blood pressure were concurrent.

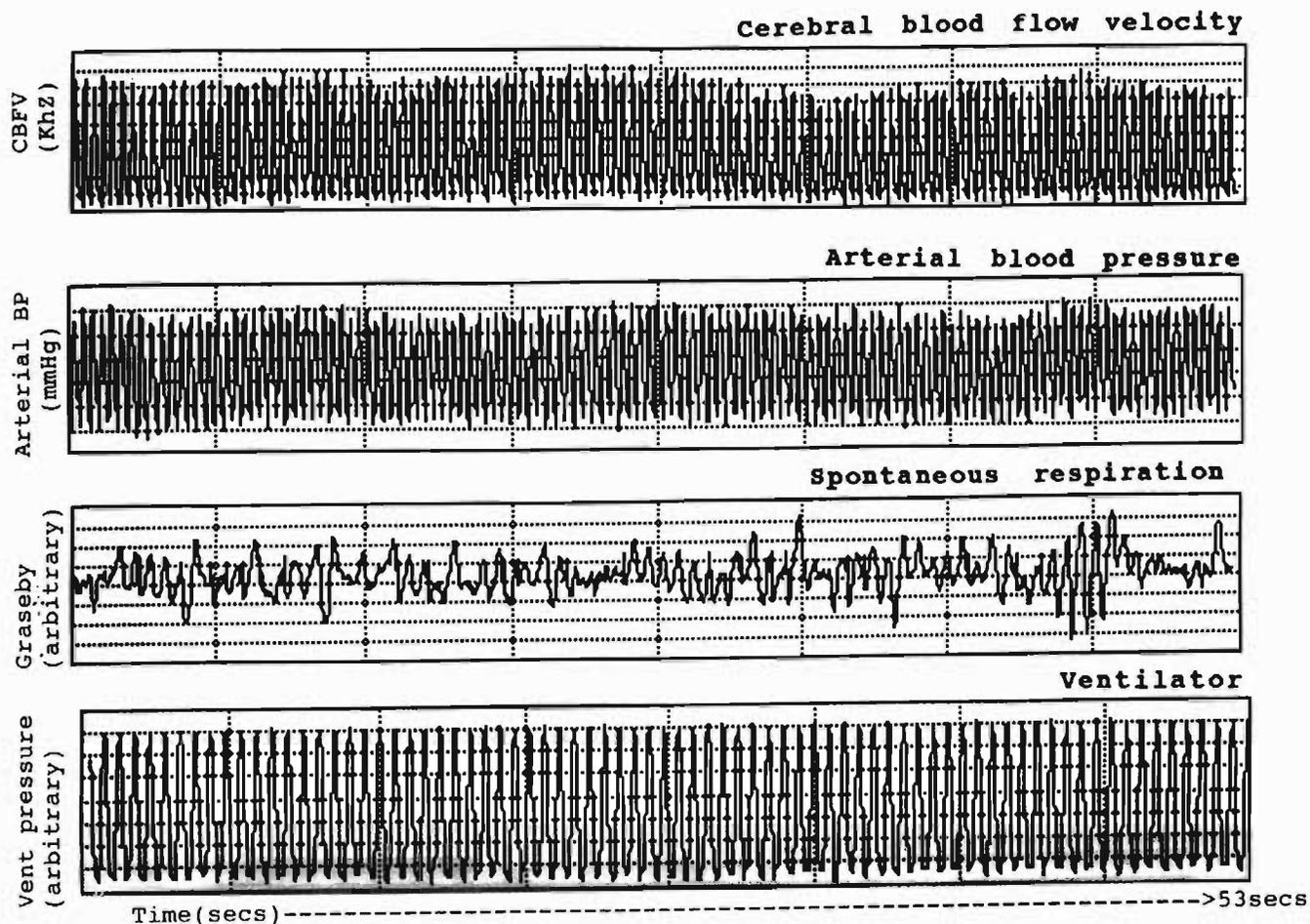


Figure 8

A recording of 4-channel raw data

The third channel represents signals obtained from a Graseby capsule. In this infant, spontaneous respiration and ventilator breaths are asynchronous.

These data were used to examine the factors which were of importance in respiratory induced variability in CBFV, as well as the associations between variability in CBFV and arterial BP, hypotension, cerebral injury, mortality rate and presence or absence of PDA. Extra recordings were made if a patent ductus arteriosus was clinically diagnosed to be present. At the same time, Doppler evidence of a PDA was sought as described.

Information concerning any drugs administered, ventilatory settings and blood gases at the time of study, were also collected, along with extensive maternal and infant factors (see later section).

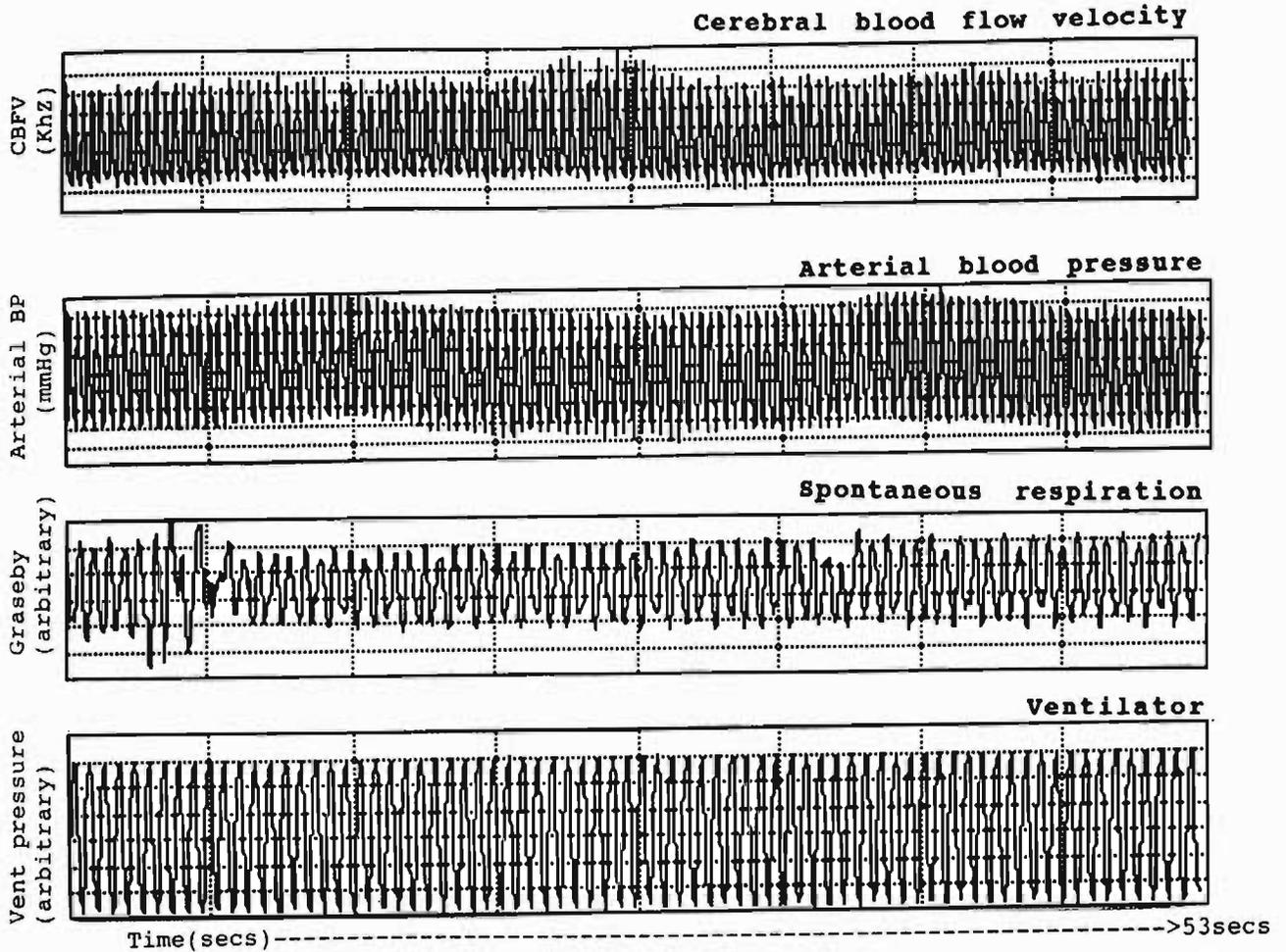


Figure 9

A recording of 4-channel raw data

The third panel represents signals obtained from a Graseby capsule. In this infant, the trace largely represents ventilator pressures. This infant was sedated at the time of study.

II.II.II. Slow fluctuations in CBFV - longterm phase.

Since low frequency fluctuations (1.5 - 5 cycles per minute) have been described in both healthy full-term and in sick extremely preterm neonates, slow variations in CBFV were

examined in this cohort of preterm infants, in a longitudinal study extending to fourteen weeks of postnatal age, to see whether any slow variations were present, and whether they remained constant over this period. This variability has been described as a normal phenomenon (Anthony et al 1991, Reynolds et al 1997).

Those infants with birthweight less than 1501 grams, who remained in the Neonatal Unit in Cambridge for longer than 4 weeks were the subjects of this study. This phase incorporated results of CBFV obtained on day 1 of life. After discontinuation of arterial monitoring, weekly recordings were made of CBFV only, along with weekly real-time images of the brain in the standard views. Again, each velocity study lasted 53 seconds, and was stored within an Apple Macintosh 2 computer running Labview as described above.

Those infants who did not require indwelling lines or artificial ventilation had day 1 and then weekly recordings made of CBFV only, as well as day 1 then weekly real-time scans.

II.II.III. Follow-up at 18 months corrected age

All surviving infants were examined and assessed using the Bayley scale of mental and motor development, at 18 months post-term, corrected for prematurity.

Cerebral blood flow velocity measurements used in this analysis were calculated by first calculating the time-averaged velocity for each cardiac cycle by halving the maximum velocity. This has previously been shown to give the best estimate of velocity in the neonatal cerebral circulation (Evans et al 1989). The mean value over a large number of cardiac cycles - usually all of the 53 second epoch, was then calculated by integration.

This is important because of the presence of slow cycling described above.

Surviving infants were assessed at 18mths post-term (corrected for prematurity), by one experienced observer who was unaware of early ultrasound and Doppler velocity findings. All infants were examined neurologically using the method described by Amiel-Tison and Stewart (1989), then assessed using the Bayley scales of infant development (1969).

II.III. Instrumentation

II.III.I. Ultrasound instrumentation

All studies were performed by a single operator (the author). Duplex Doppler ultrasound (Advanced Technology Laboratories Mk600) was used with a pulsed Doppler flowmeter and standard settings (100Hz) were used for wall filter. The lowest power settings possible to produce acceptable images were used. Output was within the safety guidelines set by the American Academy of Ultrasound ie a maximum setting of 100 mWcm² (American Institute for Ultrasound in Medicine 1988).

This allowed 2-Dimensional real-time imaging of cerebral and cardiac structures, as well as Doppler flow studies of the anterior cerebral artery and the pulmonary artery.

Although the Neonatal Unit acquired a colour Doppler ultrasound machine during the study year, in order to standardise results, the ATL Mk600 was used throughout.

II.III.I.I. Cerebral imaging and recordings

For cerebral study, the anterior fontanelle was used for access. Using a 7.5 MHz scanhead (Rennie 1997 p7), images in the standard views (coronal and sagittal) were obtained on day 1 then weekly for each baby studied, and recorded using a Mitsubishi

video copy processor. This allowed later independent assessment of any intracranial structural abnormality, periventricular or intraventricular haemorrhage, and ischaemic lesions. Levene et al's classification(1983) was used to define degree of intracranial haemorrhage and any PVL present was classified following the descriptions of de Vries(1988).

For Doppler sampling of CBFV, the anterior cerebral artery was insonated through the anterior fontanelle using real-time ultrasound to identify the vessel in the sagittal view(see Figure 6), at a precise location and known angle of insonation. This probe site, the most anterior point before the ACA turns dorsally above the corpus callosum, was used because at that position the angle of insonation is close to zero(thus minimising the effect of wall thump) and no angle correction factor has to be made. The size of the ACA in a preterm newborn is approximately 2mm, so the Doppler sampling cursor fills virtually the whole vessel diameter and the resultant complex Doppler signal requires further interpretation.

The flow analyser processed the Doppler-shifted echoes from the selected sample volume, using Fast Fourier Transform, and displayed the result on screen as a time-frequency graph; amplitude was represented by a grey scale. An audio Doppler signal was channelled through the system's speakers. This visual and auditory information assists in obtaining an optimal signal from the blood vessel studied. Because the Advanced Technology Laboratories ultrasound machine was unable to process the signal and pass it to the computer for storage fast enough to record 53 seconds of data, an alternative was required to allow data storage.

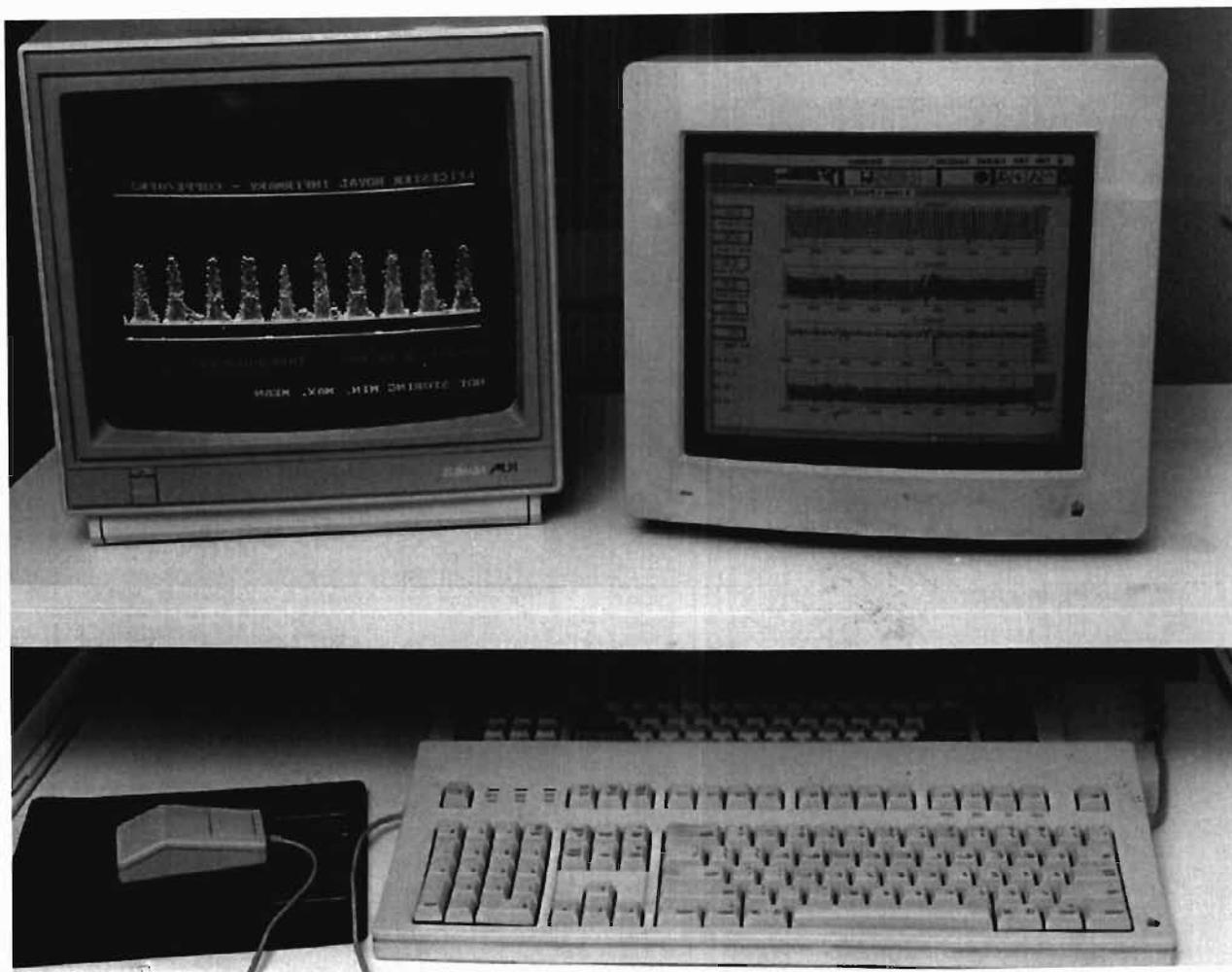


Figure 10 demonstrates - on the left, 10 frames (4 seconds) of CBFV from the anterior cerebral artery; on the right is a 53 second screen with simultaneous 4-channel recording in Labview on the right - the top panel represents CBFV, the next is arterial BP, then pressures from the Graseby capsule, and lastly ventilator pressures.

At the time this study was performed, this system allowed collection of CBFV data for only 53 seconds. The memory buffer of the computer became full at this point since a high sampling rate (every 6.25 msec) was important. Since then, technology has made significant progress, and recordings of CBFV have been collected for up to twenty-one minutes (Zernikov et al 1994).

The signal obtained for 53 seconds was processed by a microcomputer-based system developed by Schlindwein and

Evans(1989), which used Fast Fourier Transform to calculate peak velocity every 6.25 msec. The result was passed to a second microcomputer, an Apple Macintosh 2 running Labview, where it was stored for later retrieval and analysis. Pictures of the equipment are demonstrated in Figures 10 and 11.

II.III.I.II. Studies of the pulmonary artery

Duplex Doppler ultrasound was used to visualise the aorta and main pulmonary artery in a parasternal short-axis view. Diastolic ductal flow into the main pulmonary artery was considered diagnostic of PDA(Stevenson et al 1980). Disturbed CBFV in the ACA with absent or retrograde diastolic perfusion as estimated by Doppler sonography was also considered diagnostic(Kupferschmid et al 1988). Since only a black and white duplex Doppler ultrasound machine was available for most of the study period, the same machine was used throughout. Diagnosis of a PDA was therefore based on older criteria rather than the more reliable visualisation and flow measurements available with a colour Doppler machine(Skinner et al 2000). This method is far less able to give information concerning clinical significance of a patent duct.

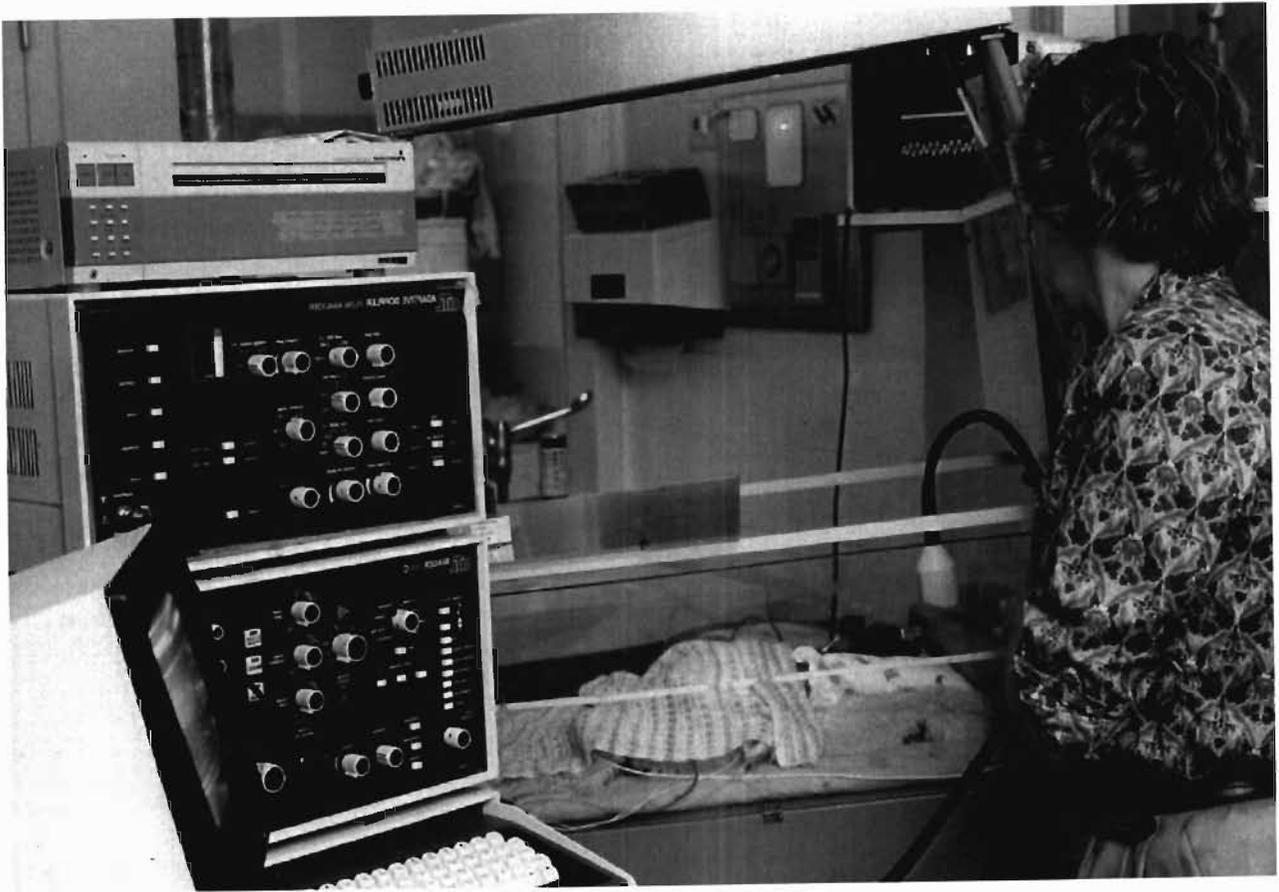


Figure 11 demonstrates a recording of a cerebral Doppler study being made on an infant in the study

II.III.II. Blood pressure recordings

Where clinically indicated, arterial blood pressure was monitored from an indwelling arterial catheter either in an umbilical artery or in a peripheral artery, via a Sorensen intraflow transducer. Two-point calibration was performed using a mercury sphygmomanometer, at the time of insertion and whenever the trace became damped. Also, a signal at a known blood pressure was used for voltage calibration.

II.III.III. Respiratory recordings

If a baby was ventilated, recordings were taken of the ventilator pressure via a mercury pressure transducer (M11), which continuously sampled the pressure administered, using a 3-way tap incorporated into the pressure-monitoring line of the

ventilator tubing. This did not give accurate pressure readings because of poor pressure response, but allowed a record of rate.

Spontaneous respiratory effort was recorded from a respiratory monitor (type MR10) via a Graseby capsule. This also did not give accurate pressure measurements, but gave a rate and also allowed us to see whether spontaneous ventilation was synchronous with the ventilator.

The analogue outputs from both respiratory recordings and that from BP, were sampled at 30 Hz, and stored along with the CBFV signal within Labview.

II.IV. Further analysis of stored recordings

II.IV.I. Acute phase

II.IV.I.I. Signal analysis

A data-tapering window in the form of a Kaiser-Bessel window was applied to each 53 second epoch recorded signals from ventilator, BP, spontaneous respiratory effort and CBFV prior to frequency analysis via fast Fourier transform(FFT).

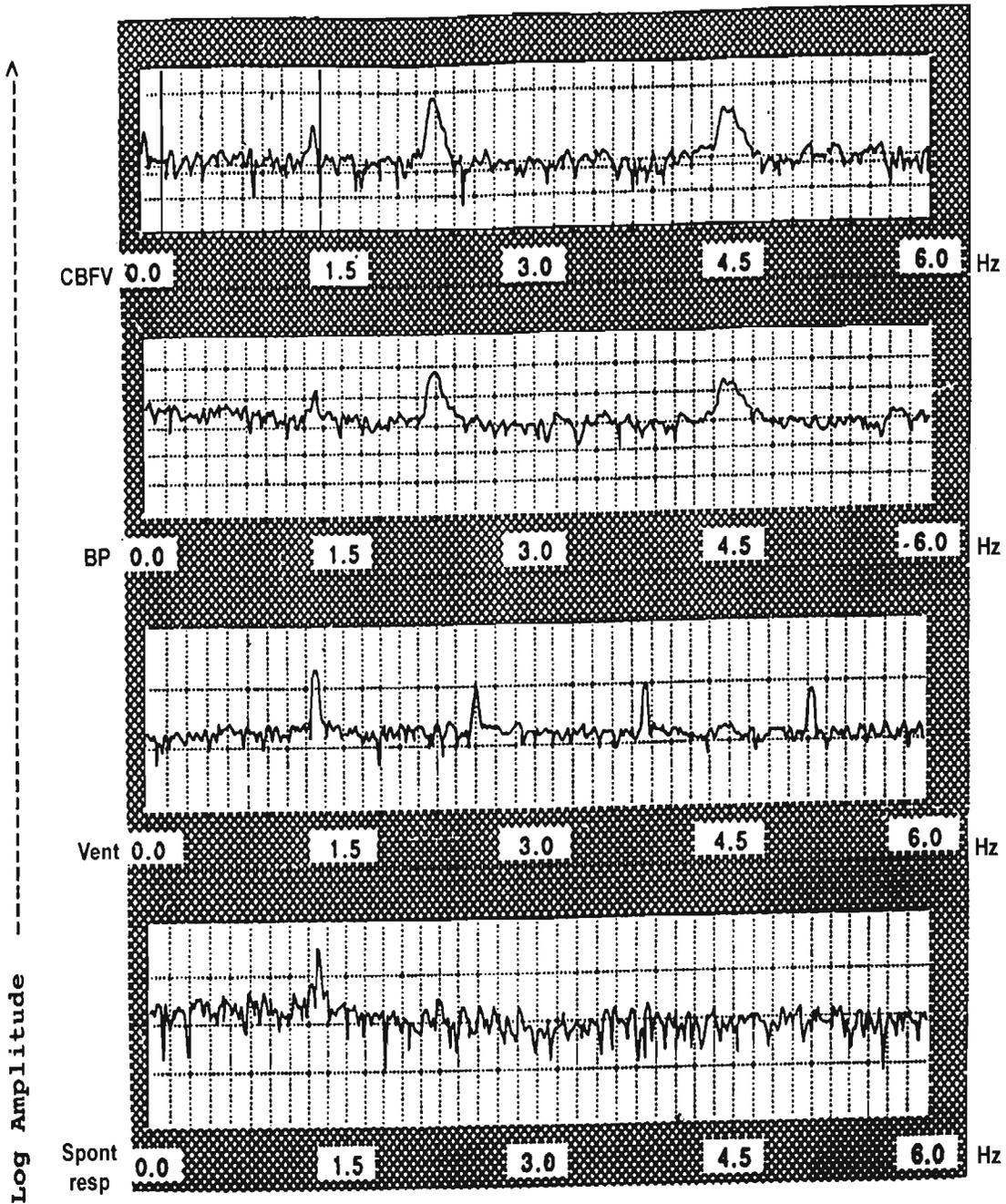


Figure 12 Spectral analysis of raw data
 Respiratory induced variability present in CBFV.
 Channel 4 represents data collected from a Graseby capsule
 and here represents both spontaneous respiration and
 ventilator pressures.
 A peak at HR frequency is seen at 2.25 Hz in the BP and
 CBFV traces. The ventilator rate is 78/min and a
 corresponding peak is seen in all channels at 1.3 Hz.

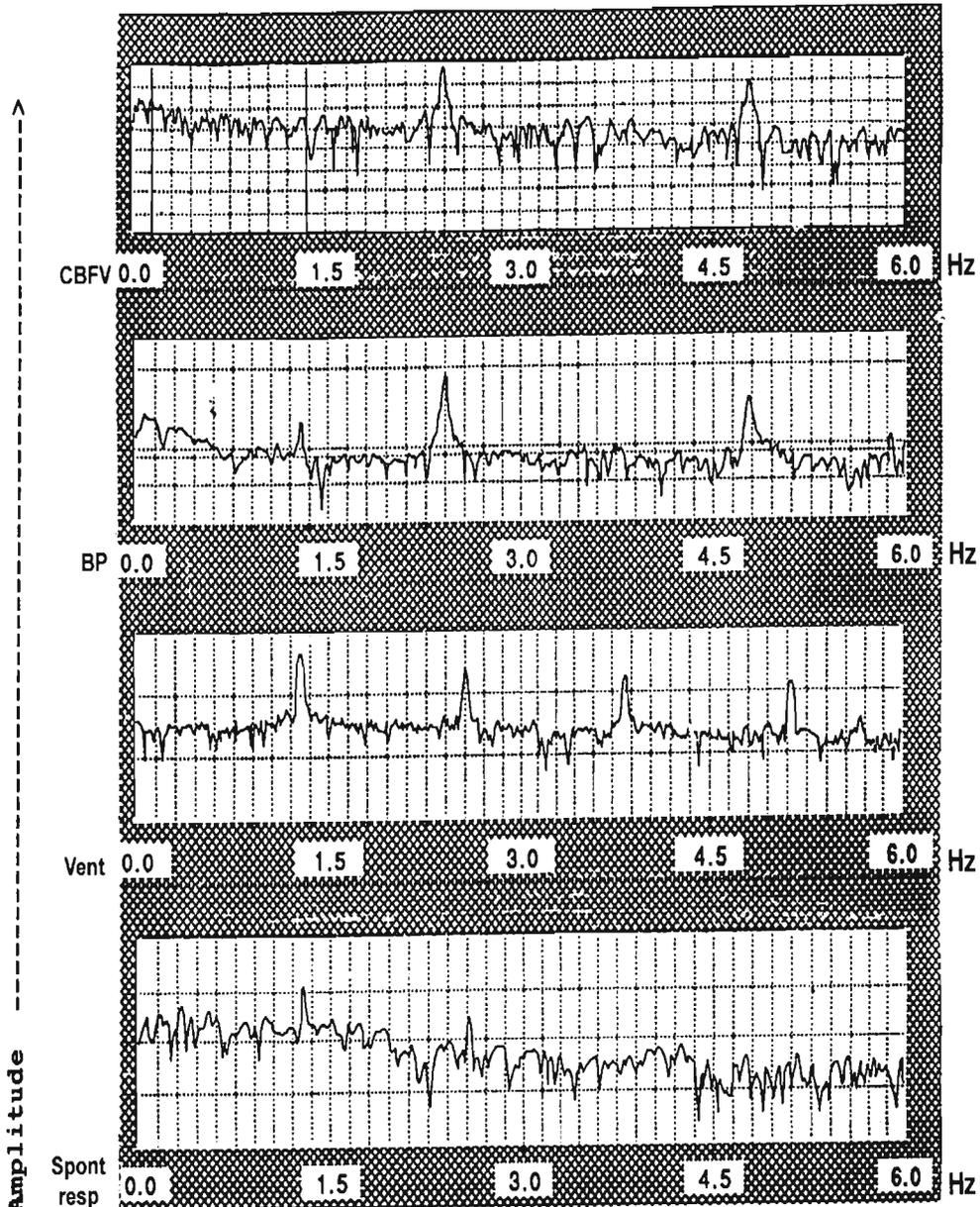


Figure 13 Spectral analysis of raw data

Respiratory induced variability absent in CBFV.

Channel 4 represents data collected from a Graseby capsule, and here represents both spontaneous respiration and ventilator pressures.

A peak at HR frequency is seen at 2.55 Hz in the BP and CBFV traces. The ventilator rate is 79/min and a corresponding peak is seen in all channels except that of CBFV at 1.3 Hz.

This technique allows a signal in time to be converted to the frequency domain. A cyclic oscillation in the measured signal is reflected in the frequency spectrum at the frequency of oscillation.

In this study, a logarithmic scale was used in order to reduce scatter. In the majority of recordings, spectral analysis enabled the identification of 2 different responses.

The classification was awarded based on visual impression. This was done jointly by 2 people (the author and an independent person). Where agreement could not be reached on which response was present, the recording was deemed unclassifiable. All classification was made with numbers, not names attached to the traces and in the absence of any accompanying clinical information.

In the first response possible, a peak was visible at either the spontaneous or ventilator respiratory frequency in both BP and CBFV traces. Another peak was seen at the HR frequency (Figure 12). In the second response, the power of the spectrum of the heart rate was the same in both BP and CBFV traces, but no peak at either the spontaneous or ventilator respiratory frequency was seen in the CBFV (Figure 13).

II.IV.I.II. Coefficient of variation

For each one minute epoch of recorded signals from BP and CBFV, the coefficient of variation for the area under the velocity curve of 20 successive cardiac cycles was calculated, and a 20 cycle moving window then applied to the whole recording. This allowed identification of the range of the coefficient of variation (expressed as a percentage) of CBFV and BP over the period of one minute in each individual. Software

for this analysis was again provided by Paul Scrivens and Hugh Dangerfield(BA^eSEMA) within the Labview programme.

II.IV.II. Slow fluctuations in CBFV- longterm phase

Each recording made of CBFV, lasting 53 seconds was subsequently visually inspected. This was done by the author and one other. To minimise bias, neither the name of the baby nor any clinical details were linked to the recordings at the time classifications were made.

Each trace was classified as

- a) showing variations at a frequency of between 1 and 5 per minute,
- b) showing no such variations, or
- c) unclassifiable.

Figure 14 demonstrates slow variations up to and including 34 weeks, the 36 week recording is unclassifiable and there are no slow variations at 39 weeks. Figure 15 shows subsets from the same baby.

Variations at frequencies above 5 per minute, probably due to the influence of respiration, were not considered in this study.

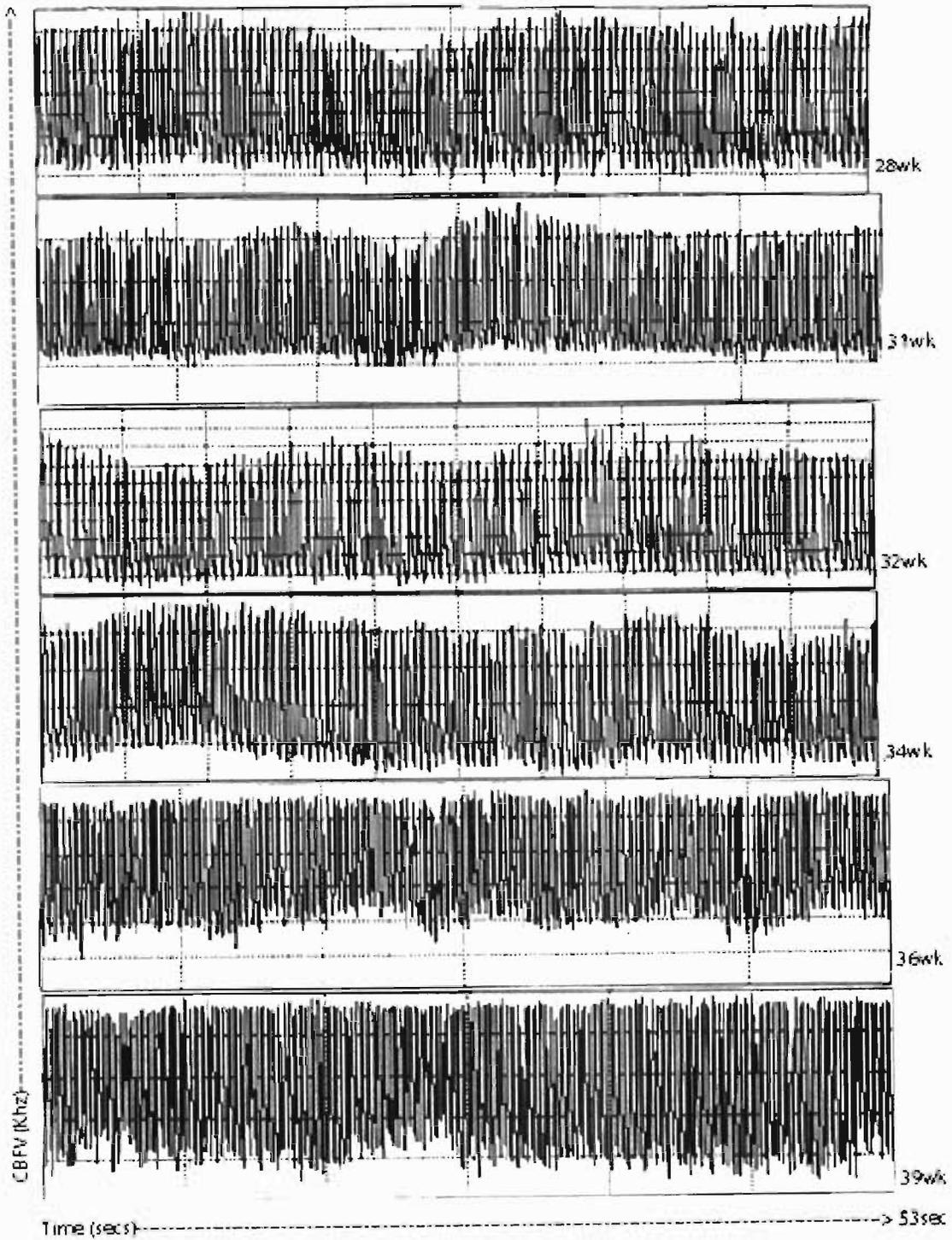


Figure 14 Evolution of slow cyclical variations.

Each panel represents 53 seconds of data.

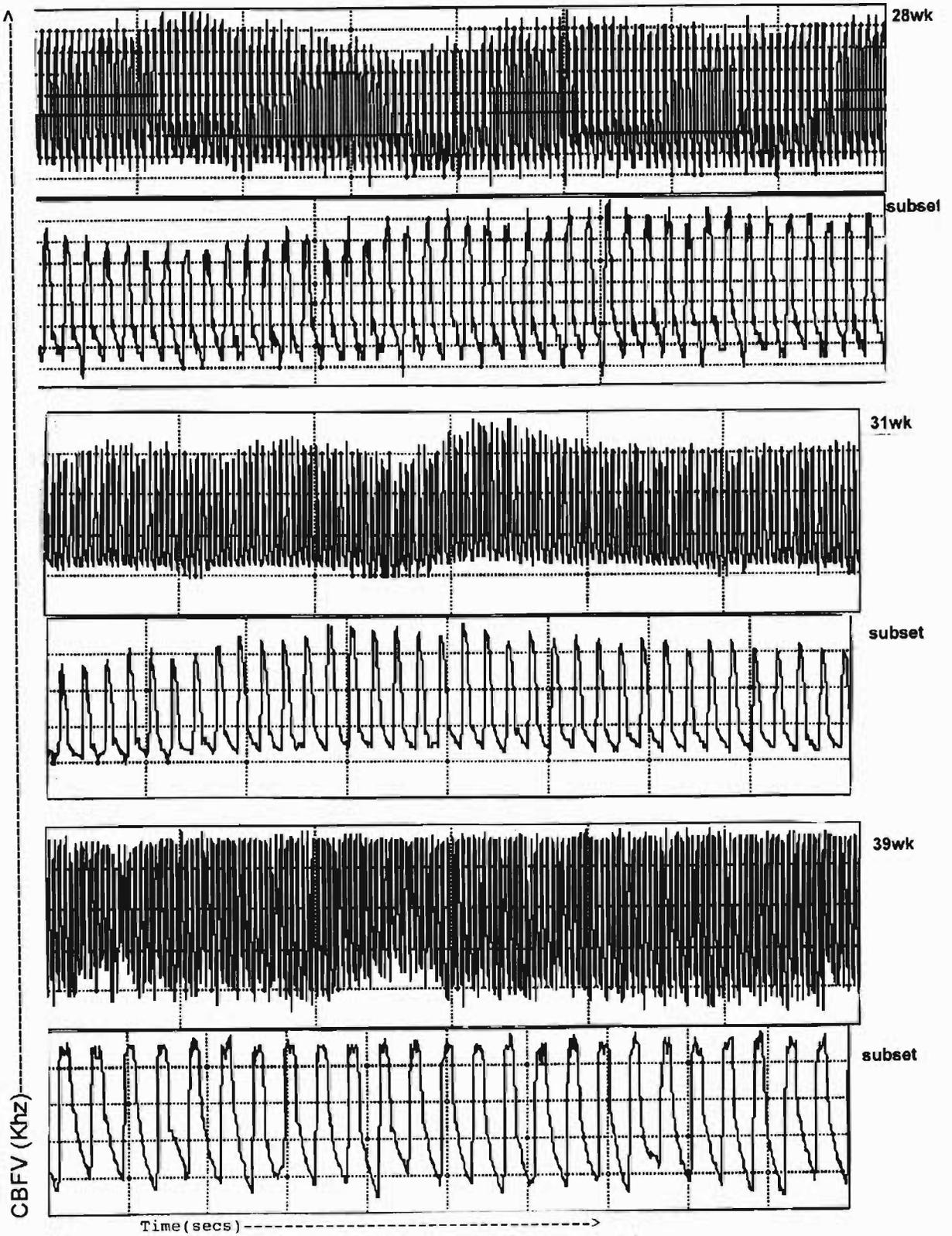


Figure 15 Evolution of slow cyclical variations
Each subset lasts a fraction of 53 seconds

Amplitude of variability was then calculated by using the maximum systolic velocity present in the whole recording, subtracting the minimum systolic velocity, and dividing by the maximum systolic velocity. This was then expressed as a percentage.

The visual classification of slow variations was validated by comparing visual inspection with calculated values of maximum variation. A value of less than 10% maximum variation was used as a cut-off for comparison with visual classification of no slow variation, as previous work has shown that short term variability is usually less than 10% (Rennie 1989, Perlman et al 1983).

II.IV.III. Follow-up study

Infants surviving to 18 months post-term were assessed by an independent Paediatrician to see whether CBFV measurements made early in life were of predictive value.

II.V. Data collection

All data concerning each baby was collected prospectively. An example of the data collection sheet is shown in Appendix 1. A record was kept of ventilator pressures, rates and oxygen requirements at the time of study. Factors of particular interest included gestational age and birthweight, severity of illness, episodes of hypotension and use of inotropes, use of sedatives, agents of paralysis, other medications, ductal patency and ultimate outcome including intracranial injury incurred. Extensive information was also collected concerning maternal, antenatal and neonatal factors.

II.VI. Statistical analysis

All statistical analysis was reviewed by an independent statistician. Once collected, records were stored within a database (Statistical Package for the Social Sciences Data Entry). This data was then analysed using SPSS - a comprehensive, integrated system for statistical data analysis.

When exploring the factors which may have been associated with the appearance of respiratory-associated variability in CBFV, logistic regression was used. This form of statistical analysis was chosen because the dependent variable was a dichotomous categorical variable. Fisher's exact test and *t* tests were also used to compare groups before logistic regression.

Non-parametric tests (Mann Whitney U) were used to examine the relationship between the variability of systemic BP and that of CBFV, and also the association between CV% of CBFV and the factors outcome, hypotension, brain injury and the presence or absence of a patent ductus arteriosus.

SPSS was again used to analyse the results of the blinded follow-up.

Chapter III. Results

III.I. Description of perinatal factors

A consecutive cohort of 74 babies of birthweight less than 1501 grams was admitted to the Special Care Baby Unit at the Rosie Maternity Hospital in Cambridge. There were no omissions and no parent refused consent.

Relevant demographic data is shown in the tables below.

III.I.I. Characteristics of babies(a)

Singletons	56
Twins	7 sets, 3 sets- one twin in study
Triplets	1 set- 1 triplet in study

III.I.II. Characteristics of babies(b)

	Median	Range
Gestational Age (wks)	29	24 - 33
BWt (grams)	1173.5	501 - 1499
Apgar ¹	5	1 - 9
Apgar ⁵	8	3 - 10
Maternal age (years)	26	17 - 42

III.I.III. Relevant Antenatal Factors

Nil	43 (58.1%)
Maternal systemic disease	2 (2.7%)
Prolonged membrane rupture	6 (8.1 %)
Maternal hypertension	13 (17.6%)
Antepartum haemorrhage	10 (13.5%)

III.I.IV. Intrapartum Factors

Sepsis	5 (6.8%)
Presentation	
Cephalic	52 (70.3%)
Frank breech	6 (8.1%)
Footling breech	12 (16.2%)
Transverse lie	4 (5.4%)

III.I.V. Mode of Delivery

Spontaneous vertex	19 (25.7%)
Spontaneous breech	2 (2.7%)
Vertex forceps	3 (4.1%)
Breech forceps	3 (4.1%)
Emergency C/S	37 (50%)
Elective C/S	10 (13.5%)

III.I.VI. Postnatal Factors

Sepsis	- Proven	2 (2.7%)
	- Suspected	6 (8.1%)
Surfactant	- Nil	17 (23%)
	- Given	57 (77%)

III.I.VII. Cardiovascular compromise

Any hypotension	17/74 (23%)
Inotropes given	20/74 (27%)
PDA detected	22/66 (32%)

III.I.VIII. Outcome

Cerebral injury	
Nil	54 (73.0%)
Grade 1,2 IVH	10 (13.5%)
Grade 3,4 IVH	8 (10.8%)
PVL	2 (2.7%)
Deaths 1st week	9 (12%)
Deaths >1week prior to discharge	4 (5.4%)
Later deaths(discharge to 18 mths)	2 (2.7%)

III.II. Cerebral blood flow velocity variability in the first week of life**III.II.I. Factors associated with respiration induced variability in cerebral blood flow velocity**

Two hundred and forty nine recordings were made from 74 infants. Each recording consisted of a 53 second epoch of simultaneous signals from ventilator, blood pressure, spontaneous respiratory effort and cerebral blood flow velocity(4-channel recordings). The timing of recordings was widely variable but generally for the first 3 days, recordings were made 24 hours apart. Examples of such recordings are seen in Figures 8 and 9. Thirty seven infants were studied on all 4 days(days 1,2,3 and 7), with the remainder contributing fewer epochs due mainly to early death. Eight infants had 5 sets of recordings made because a separate epoch was collected at the time when a clinical diagnosis of patent ductus arteriosus was made, in view of the possibility that this would influence

CBFV. Figure 16 shows the number of observations made for each infant.

No infant was bradycardic ($HR < 100$ /minute) during a recording. Ventilator rates varied from 15 to 150 per minute.

Spectral analysis of the 4-channel recordings yielded 2 different responses as described (presence or absence of respiratory induced variability). Examples of these are seen in Figures 13 and 14.

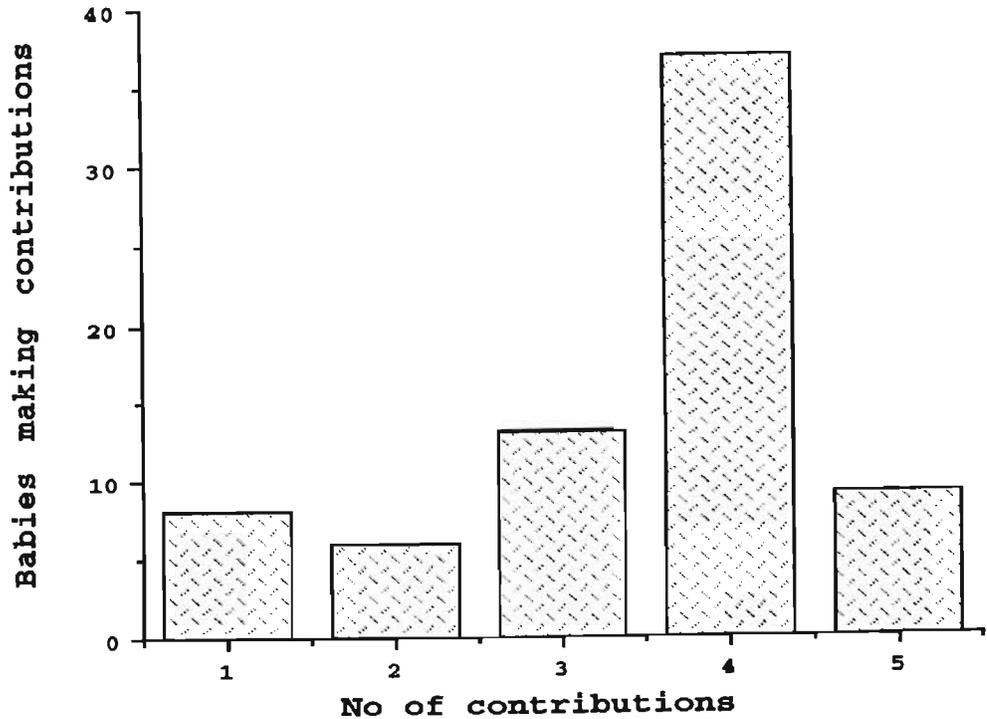


Figure 16
Number of observations made on each infant

Figure 17 shows the distribution of responses over the first week of life. The 2 responses were approximately equally distributed. Individual babies showed different responses on different days.

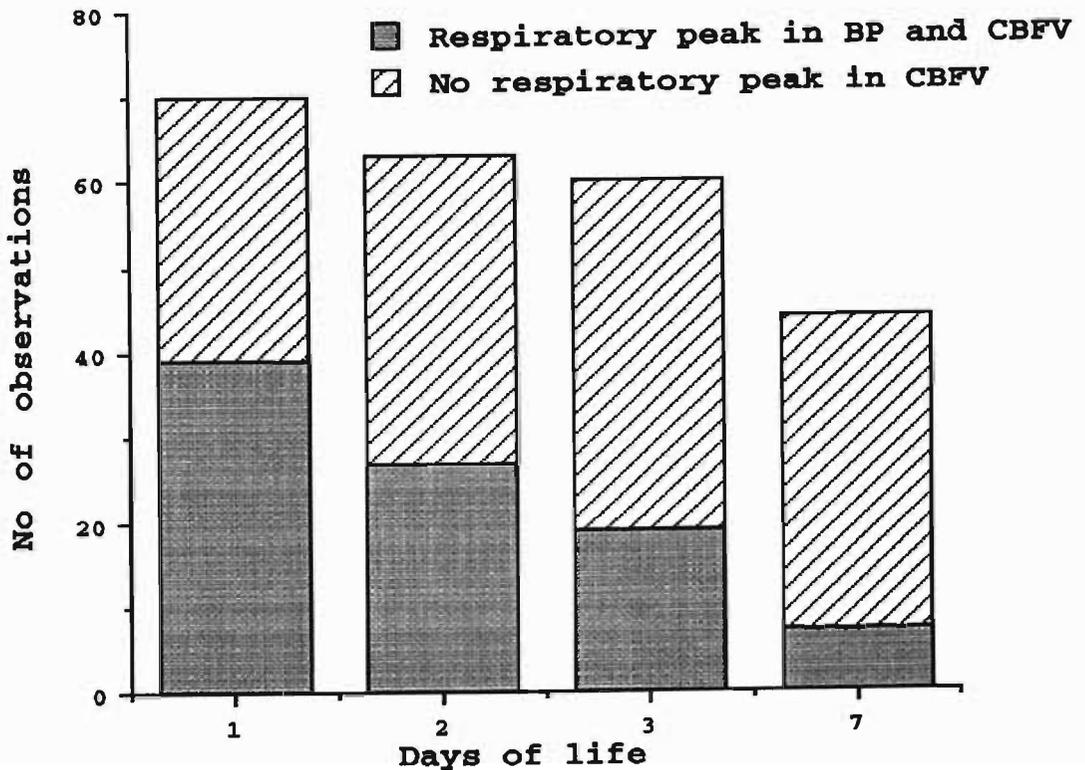


Figure 17
Distribution of responses over the first week of life

The presence of respiratory associated variability in CBFVV was seen in 47 of the 74 infants at any one time. It was most likely to be present on the first day after birth, being present at this time in 40 of 70 infants studied, and occurred less often as the first week of life progressed. On the first day of life, 4 infants had recordings which were technically unsuitable for analysis.

Thirty seven of the infants demonstrating respiratory associated variability in CBFVV were ventilated at this time, versus 19 of those who did not show respiratory induced variability ($\chi^2 = 12$; $p < 0.005$). Even in ventilated infants, however, the frequency which was represented in the CBFV was

more likely to be the spontaneous respiratory frequency rather than the ventilator frequency if the two were different; in 106 of 137 epochs recorded in ventilated infants, the spontaneous and ventilator frequencies were the same because of the policy to try to use synchronous ventilation where possible or else because the infant was sedated or muscle relaxed. The trend for a decrease in respiratory induced variability over time is statistically significant ($\chi^2 = 23$; $p < 0.0001$).

To explore the influence of associated variables, these data were examined further in two ways.

III.II.I.I. Factors related to the epoch when respiratory induced variability was noted

Firstly, to explore the influence of ventilator settings, blood pressure and blood gas variables during separate epochs, each recording was considered as a separate case. This allowed an analysis considering information pertaining to the situation at the time of the study, but most infants contributed more than once to this data set (Fig 16). Some of the variables available for analysis are shown in Table 7.

Two hundred and forty nine epochs were available for analysis. Using FFT, ninety seven showed the presence of a respiratory frequency in cerebral blood flow velocity. As shown in Table 8 below, univariate analysis suggested that factors relating to artificial ventilation were the most important; blood gas results were not implicated, nor was the type of sedation used. Hypotension during the study epoch was significant ($p < 0.001$), as were the total hours of hypotension recorded during the day on which the study was made ($p < 0.002$) (see Table 8).

Table 7. Factors recorded prospectively and used in univariate and multivariate analysis

Respiratory Factors	Peak pressure Rate Hours in oxygen Percentage inspired oxygen Arterial blood gas results
Circulatory factors	Blood pressure, inotropic support Cerebral injury Patent ductus Cerebral blood flow velocity cm/sec
General details	Maternal illness Mode of delivery Sex, gestation, birthweight Sepsis, Outcome

Logistic regression analysis showed that whether the infant was ventilated or not was the most significant factor, doubling the odds of the infant being in the group with any respiratory frequency represented in the cerebral circulation. The effect of ventilator rate was wholly accounted for by whether or not artificial ventilation was used; in other words, there was no independent effect of rate. The inspired oxygen concentration also had a highly significant independent effect on the type of response; for every additional 10% increase in inspired oxygen there was an increase in odds of the respiratory frequency appearing in the cerebral blood flow velocity of 1.4:1. The effects of ventilation and oxygen were not accounted for by

birthweight or gestational age. Hypotension was not shown to have an independent effect.

Table 8. Factors related to the presence of respiratory variability in CBFV by epoch

	Respiratory variability		Uni- variate p value
	Present (n=97)	Absent (n=152)	
BP <30mm Hg during study	8	0	<0.001
Hours per day BP<30	1.41±3.8	0.16±0.8	<0.002
CBFV (cm/sec)	9.9 (7.7-12.9)	11 (7.8-15.2)	0.2
Peak vent pressure (cm H ₂ O)	16 (14.5-21.5)	0 (0 - 16)	<0.0001
Inspired O ₂ (%)	50 (32-70)	21 (21-30)	<0.0002
Ventilator rate	65 (30-80)	0 (0 - 20)	<0.0001
Ventilator epochs	72	55	<0.0001
Synchronous ventilation	64	42	0.05

III.II.I.II. Factors related to the presence of respiratory variability in cerebral blood flow velocity by baby

Next the factors regarding the infants clinical course and outcome were examined related to whether or not the infant ever showed respiratory induced variability at any time. Each infant contributed only once to this data set.

Table 9. Factors related to the presence of respiratory variability in CBFV by baby

	Respiratory variability		Univariate p value
	Present (n=47)	Absent (n=26)	
Mean(SD) Bwt (grams)	1088 (243)	1259 (227)	0.004
Mean(SD) gestation(weeks)	27 (1.8)	29.4 (2.4)	0.002
Mean(SD) days in oxygen	5 (48.3)	1 (22.2)	0.04
Death	11	0	0.007
ICH Grade 2+	10	0	0.01
PVL	2	1	NS
BP <30mm Hg ever	17	4	0.05

Univariate analysis suggested that the infants who showed respiratory associated variation were smaller, less mature, and more likely to be ventilated using a higher peak pressure, rate and inspired oxygen concentration. They were more likely to die or sustain brain injury than those who never showed such a variation in their brain blood flow. There were more infants who were hypotensive at any time in the respiratory associated variability group ($p=0.05$) (see Table 9). Logistic regression analysis showed that gestational age was the most significant factor ($p=0.0018$), and that when the other factors were considered together with gestational age they did not have a significant independent effect.

III.II.II. The relationship between cerebral blood flow velocity variability and arterial BP, presence or absence of a patent ductus, cerebral injury and outcome

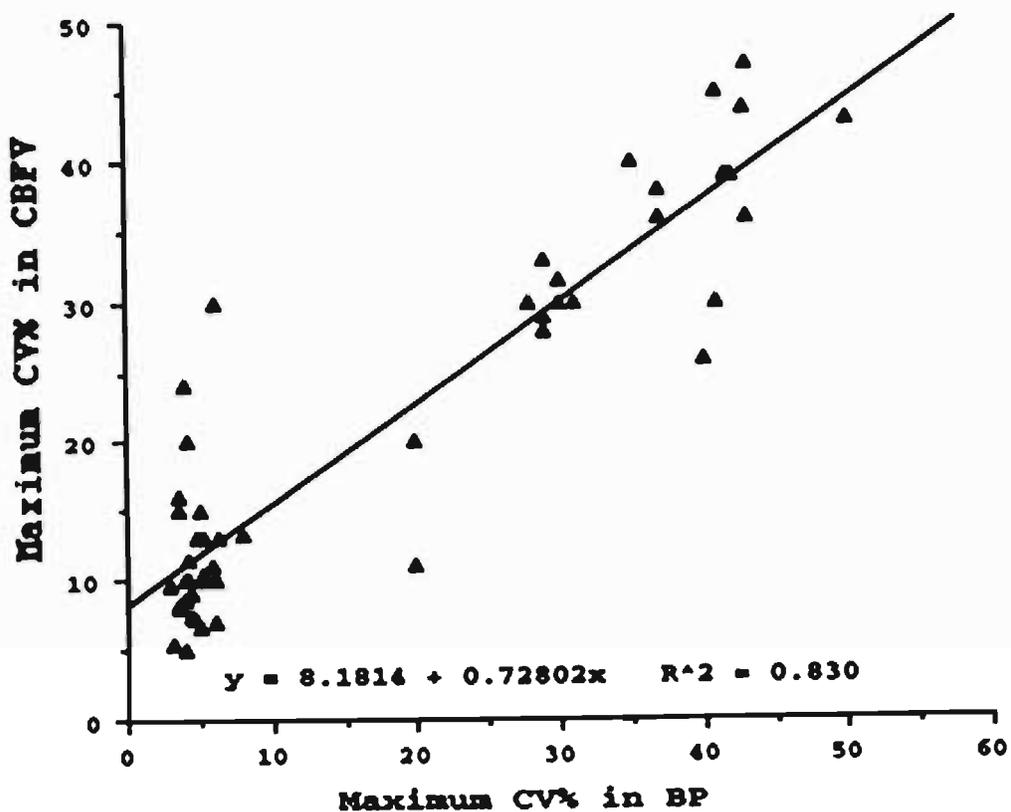


Figure 18
Maximum CV% in CBFV versus blood pressure on day 1

Recordings were obtained from 52 babies of median birthweight 1160g(range 501-1499g) and median gestational age 28.5 weeks(range 24-32 weeks). All babies in this part of the study were being ventilated and had indwelling arterial lines. All had a wide spread of CBFV variability over one minute. In this group, the maximum CV% of CBFV lay between 2% and 28%.

There was a strong correlation between variability of CBFV and that of arterial BP. This was true whether maximum(Figure 18, $r^2=0.83$) or minimum(Figure 19, $r^2=0.78$) CV% values were

employed. Table 10(below) shows the correlation between CBFV and BP during the first week of life.

Table 10. Correlation between CV% in CBFV v BP

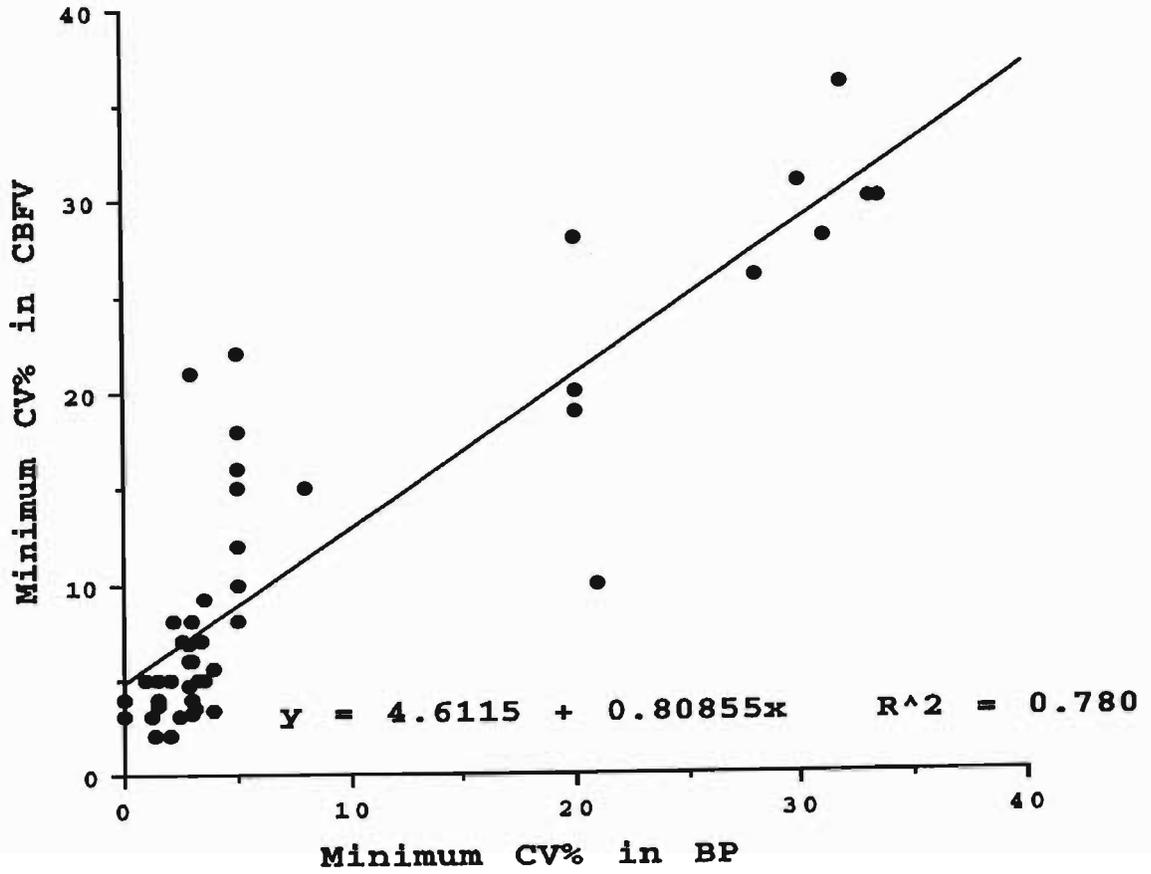
	Maximum CV%	Minimum CV%
Day 1	R ² =0.83	R ² =0.78
Day 2	R ² =0.65	R ² =0.66
Day 3	R ² =0.89	R ² =0.96
Day 7	R ² =0.65	R ² =0.99

The software analysis was validated by checking 3 recordings by hand using a paper window(Rennie et al 1987). Two paper windows were 53 seconds long and one was 38 seconds. Examples of comparisons were
 range 4.6 - 10.7 by hand versus 4.5 - 11.0 by programme
 range 4.7 - 9.8 by hand versus 3.2 - 4.6 by programme and
 range < 5% by hand versus < 8% by programme.

Although the comparisons were not precise, in each pair there was agreement between the categories normal(< 11%), high(> 11%) or absent.

Figures 20a and 20b demonstrate both examples of the raw data collected, and of this mirroring.

13 babies in this study had episodes of hypotension lasting for one hour or more on the first day of life. These babies had significantly higher variability of CBFV(for both maximum and minimum values) than did those who remained normotensive (p= 0.026), despite the fact that 11 of these 13 hypotensive infants received inotropic support(Figure 21).



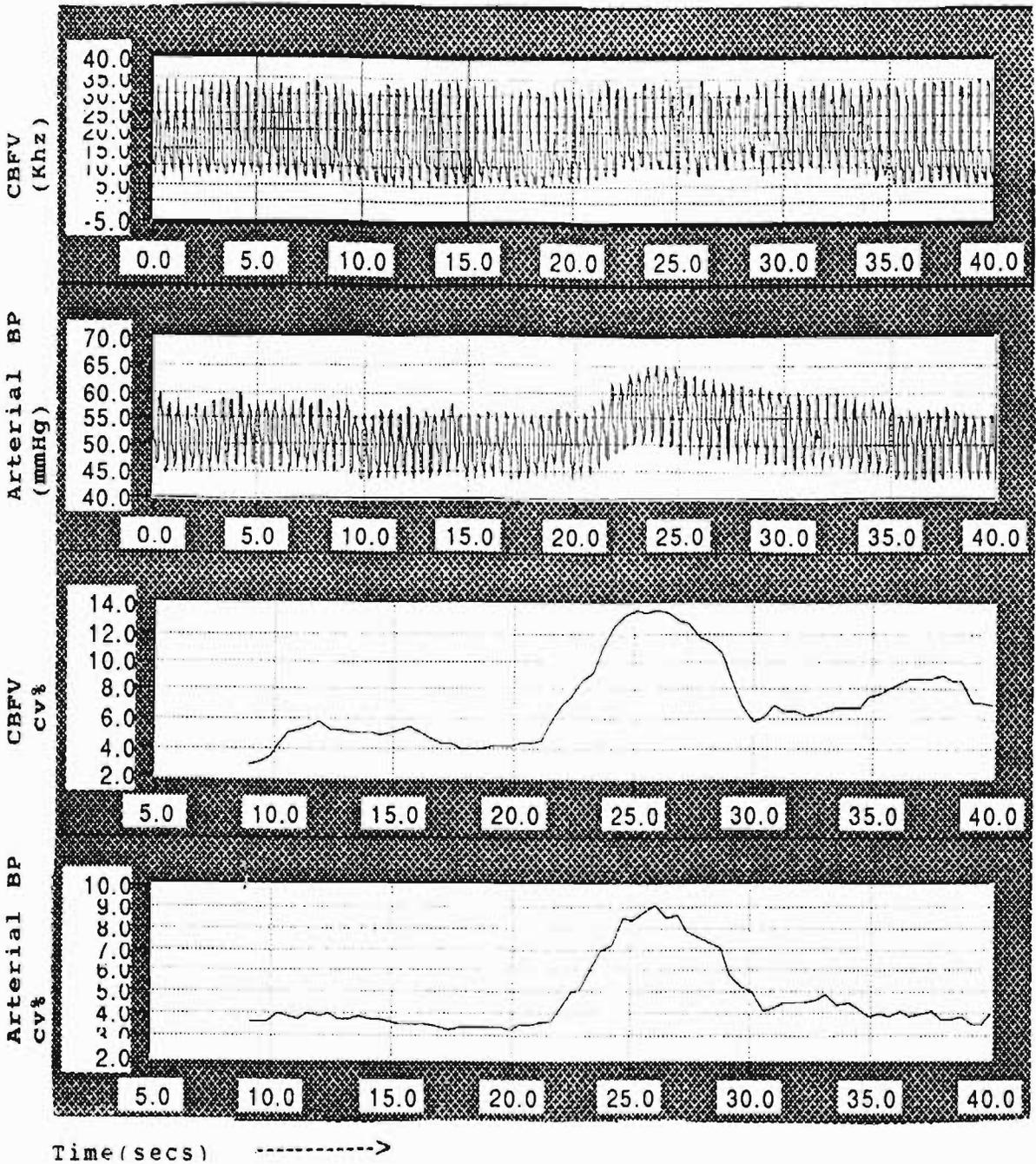


Figure 20a
 Raw data and CV% of both CBFV and BP showing the mirroring which occurs

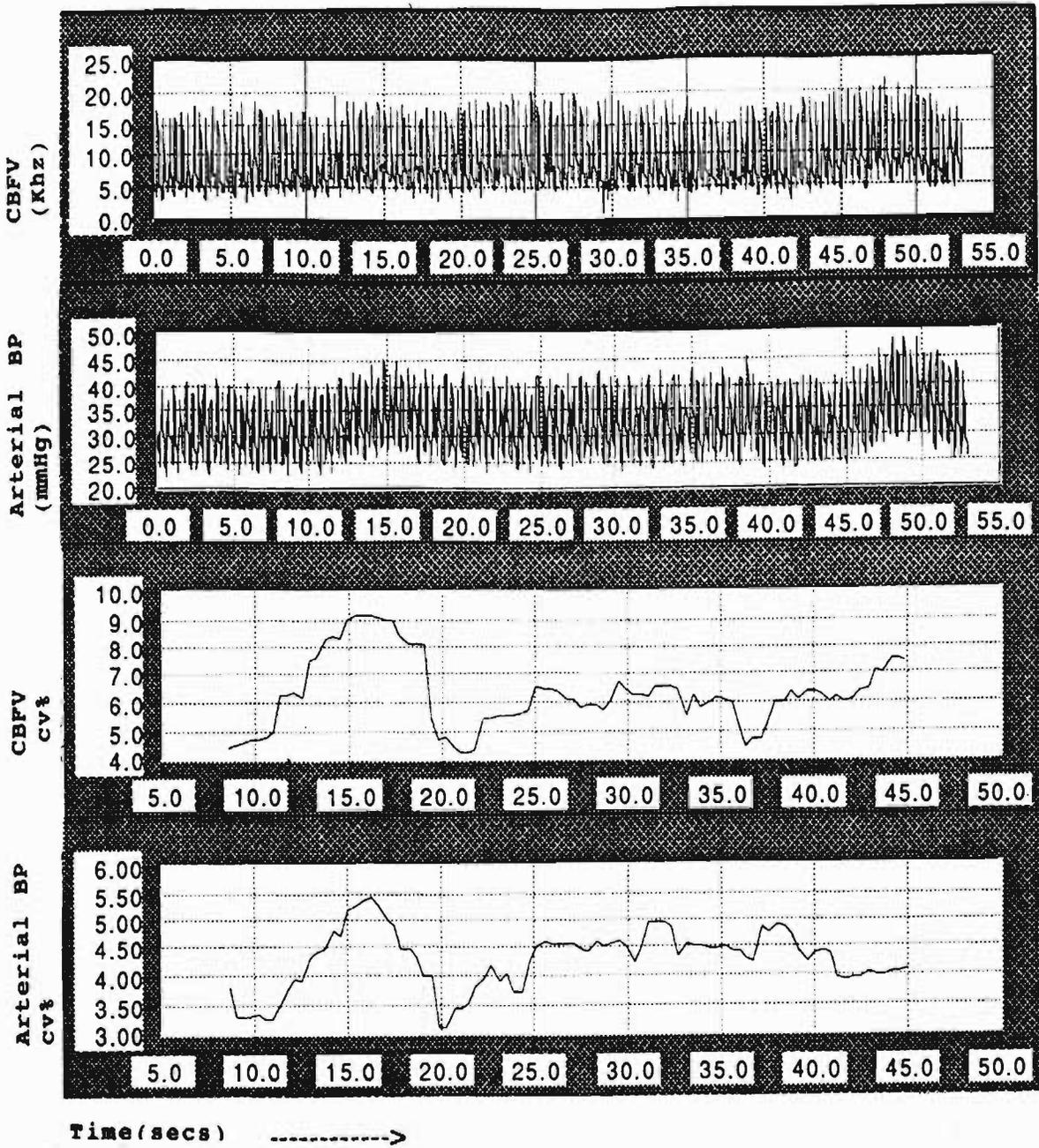


Figure 20b
 Raw data and CV% of both CBFV and BP showing the mirroring which occurs

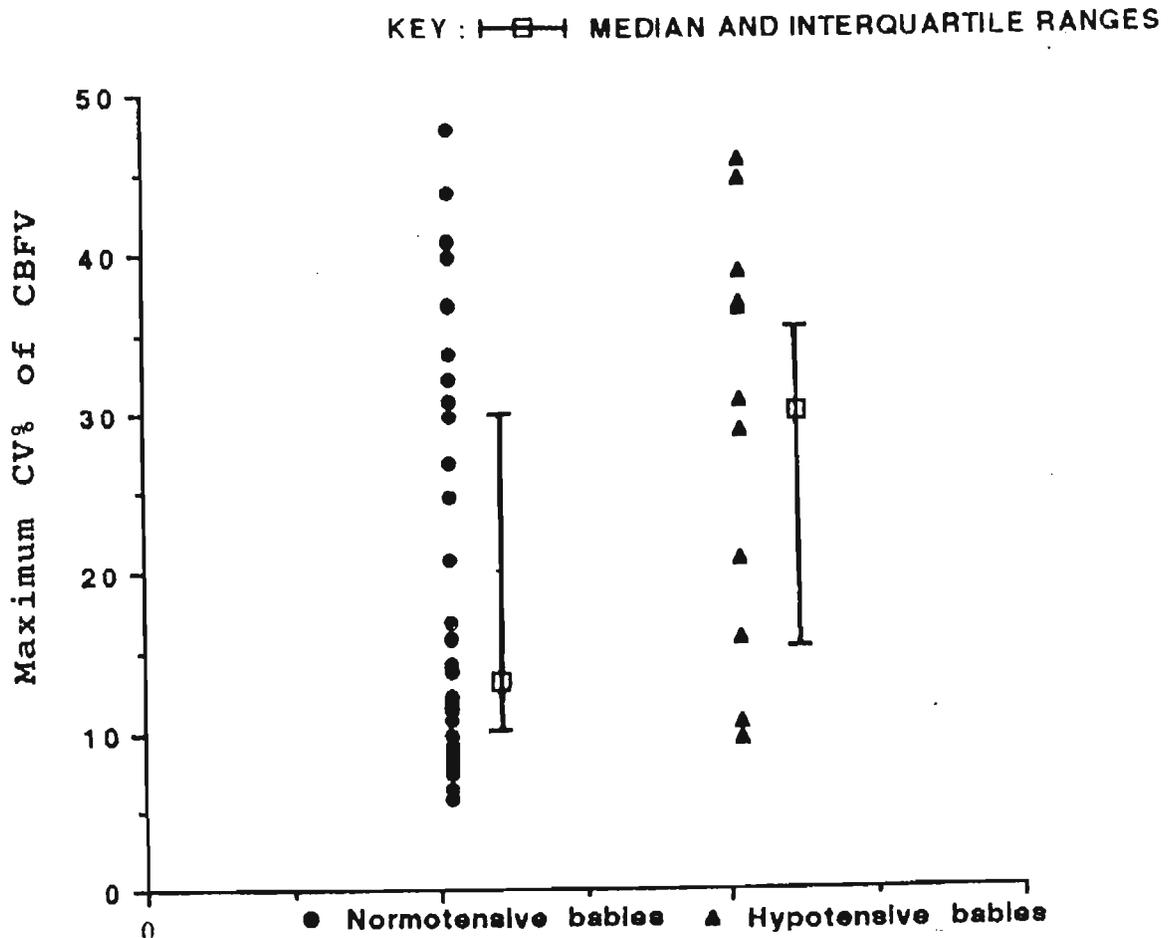


Figure 21
CV% of CBFV in normotensive v hypotensive babies

Of the 52 babies studied, 9 died, either early (within the first week) or late (greater than 1 week but less than 1 year). Babies who died had a higher maximum CV% for CBFV than those who survived ($p=0.05$). Values varied from 5% to almost 50% (Figure 22).

Six infants in this group suffered PVH of a grade greater than 2 according to Levene's classification (1983). Four infants had ischaemic lesions, 1 with huge multifocal cysts, 2 with single anterior cysts and 1 with multiple anterior cysts. However, no significant association was present between CV% of CBFV and brain injury.

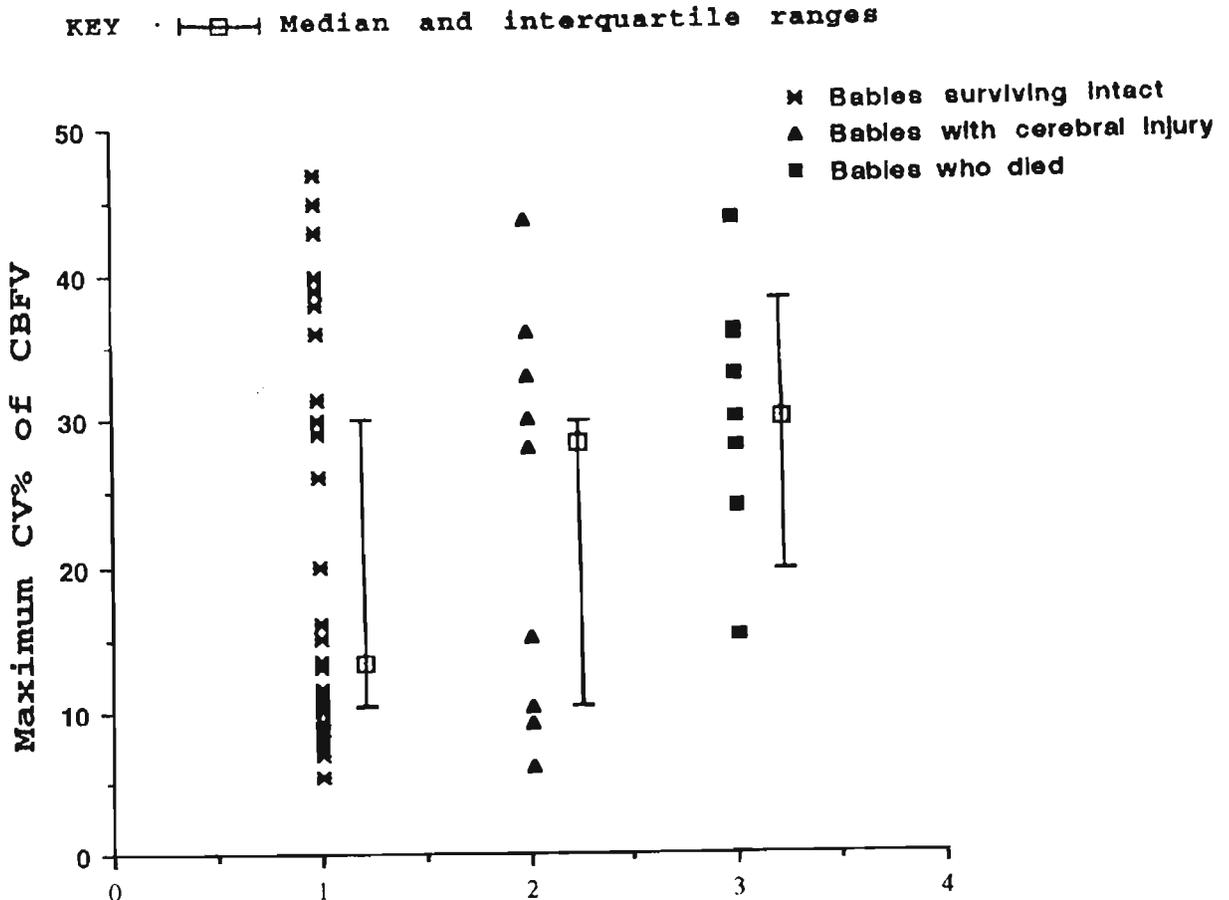


Figure 22
CV% of CBFV on day 1 versus outcome

We did find that where the CV% of CBFV was greater than 16%, the correlation between CV% of CBFV and that of arterial BP was much greater ($R^2 = 0.56$) than where the CV% of CBFV was 16% or less. This would suggest that cerebral autoregulation is less effective where the baby shows an "unstable" pattern of CV% in CBFV. Where the CV% of CBFV was less than 6% (ie perhaps abnormally low variability), correlation between CV%'s of CBFV and BP was high (1.0), but there were only 4 babies in this group.

PDA was diagnosed clinically in 13 infants and by Doppler studies in 16. No significant association was found between presence of PDA and high variability.

III.II.III. Ranges of CV% in cerebral blood flow velocity and blood pressure

Table 13 shows a sample of comparative results of CV% in CBFV and BP recordings (2 of each) obtained from the same baby during the same recording session.

Table 11. Ranges of CV% in CBFV and BP

	Range of CV% in CBFV	Range of CV% in BP
Baby A	3.6 - 8.3	3.1 - 3.5
	4.3 - 10	3.2 - 4.4
Baby B	2 - 8.6	3.2 - 7.3
	3 - 7.8	2.4 - 4.7
Baby C	5.3 - 12	4 - 20
	5.2 - 11.4	4 - 20
Baby D	30 - 42	33.5 - 37.5
	30 - 45	33 - 37.5
Baby E	5 - 10	2 - 6
	4 - 11	1.8 - 5.2

III.III. Examination of slow variations of CBFV in newborn preterm babies

III.III.I. Association of slow variations with degree of prematurity and outcome

From the cohort of 74 consecutive admissions of babies with birthweight <1500g, 30 remained longer than 4 weeks and are the subjects of this phase of the study. Table 11 shows the characteristics of these babies.

Table 12. Characteristics of babies in longitudinal study

	Median	Range	No of infants
GA (weeks)	27.7	24 - 31	
BWt (grams)	1113	573 - 1486	
Days ventilated	9.3	0.5-44	
Days in oxygen	41.1	1-2000	
PVH			
- Grade 3			4
- Grade 4			3
PVL			4

One hundred and thirty three recordings were obtained from 30 babies of mean birthweight 1113g(range 573-1486g) and mean gestational age 27 weeks(range 24-31 weeks). Postnatal age extended from birth to a maximum of 14 weeks. Babies ranged from those ventilated for less than 24 hours, to those ventilated for more than 28 days.

Six infants suffered PVH of a grade greater than 2: 3 grade 4, 3 grade 3 according to Levene's classification(1983). Four infants had ischaemic lesions, 1 with huge multifocal cysts, 2 with single anterior cysts and 1 with multiple anterior cysts. One required shunting for posthaemorrhagic hydrocephalus.

Slow variability was usually obvious, with only 4 recordings out of the 133 being unclassifiable. There was good agreement between visual classification and calculated amplitude of less than 10%(see table 13).

Table 13. Comparison of visual inspection compared with measured amplitude of slow variation

Validity of visual classification

	Slow variability present	Slow variability absent
Maximum change in systemic velocity <10%	3 (false positive)	54 (true positive)
Maximum change in systemic velocity >10%	157 (true negative)	11 (false negative)

Positive predictive value 94.7%

Negative predictive value 93.5%

Efficiency 93.8%

False positive 1.9%

False negative 19.3%

III.III.II. Evolution of slow variations with increasing postconceptional and postnatal age

Slow variations were sometimes present for only part of the minute recorded. When more than one cycle was observed, the cycle length was not always the same, meaning that the variations were not occurring at a constant frequency. The occurrence of slow variations decreased with increasing postconceptional age. All babies showed slow variations up to 26 weeks postconceptional age, whereas this was observed in only 70% at 32 weeks and at 37 weeks this had fallen to 25% (Figure 23). Ninety-five percent confidence intervals for this trend showed a significant reduction with increasing gestational age, as seen in Figure 24; babies have been divided into 4 groups of

increasing gestational age. Each group contained approximately equal numbers of babies.

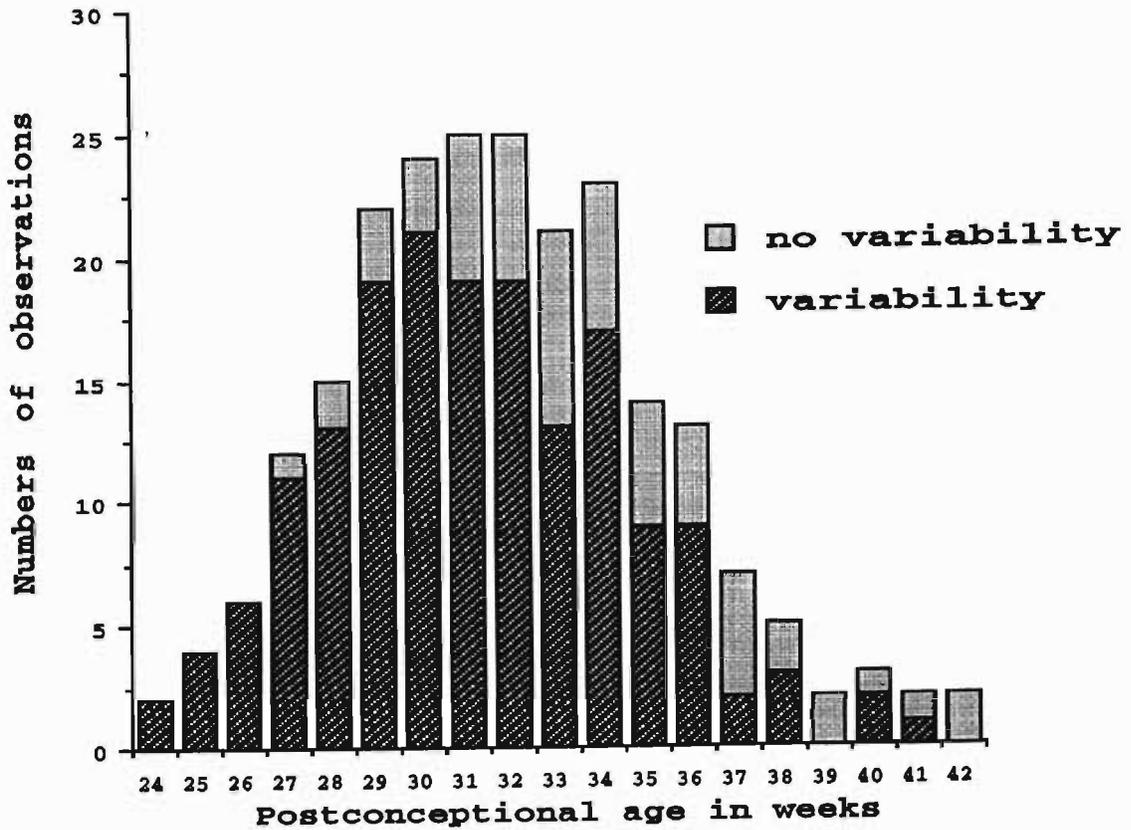


Figure 23
Presence of slow variability in cerebral blood flow velocity related to postconceptional age

A similar trend was seen with respect to postnatal age; the proportion showing epochs of no slow variations increased with increasing postnatal age. When 95% confidence intervals were calculated, there was a significant difference between groups 1 and 3 and between groups 2 and 4 (Figure 25). In this instance, groups consisted of babies of increasing postnatal age divided into 4-week periods.

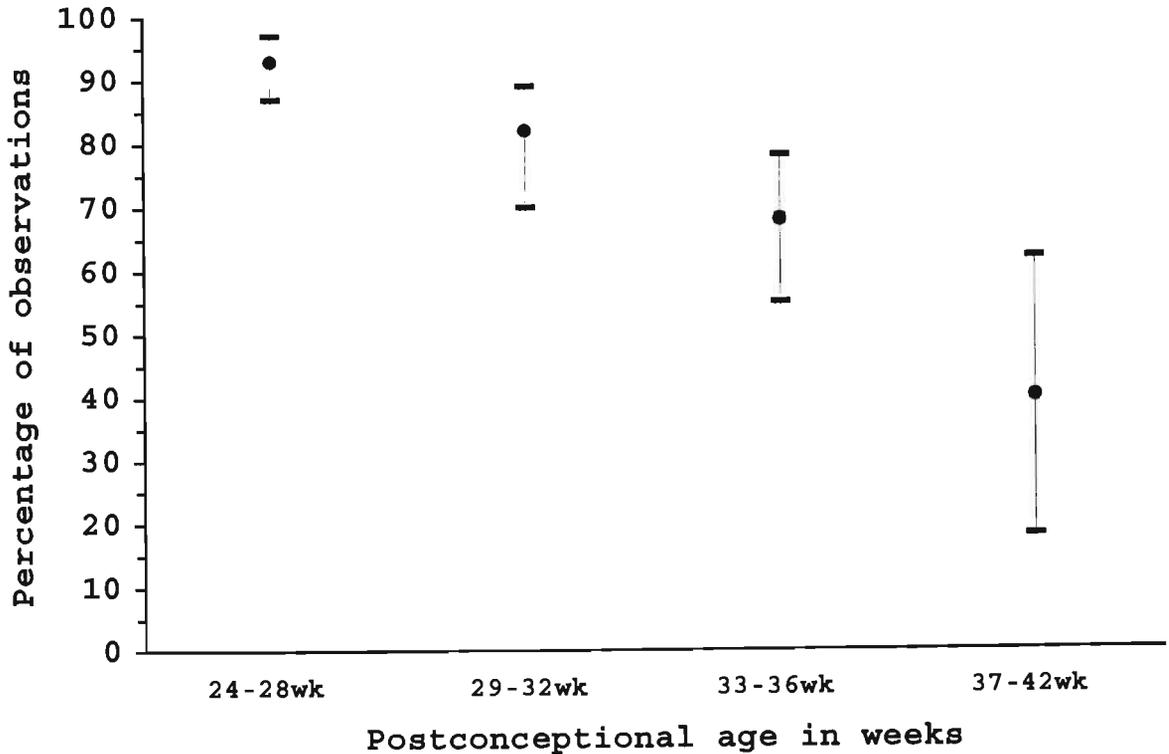


Figure 24

Presence of slow variability in CBFV related to postconceptional age, showing percentage incidence and 95% confidence intervals

There was also a significant trend for damping of the amplitude of slow variability with increasing postconceptional age and with increasing postnatal age. Regression analyses of decreasing amplitude of variation with increasing age showed a significant correlation coefficient for 7 of the 8 babies with more than 9 recordings. Figures 14 and 15 show the epochs of CBFV recorded from a single baby over 11 weeks. Regression analysis of the percentage amplitude of variability with increasing PCA in the baby shown in those 2 figures gave an r^2 of 0.45 and a $p = 0.01$. The percentage amplitude of variability was 35.9(28wk), 13.1(29wk), 25.7(30wk), 21.0(31wk), 23.3(32wk),

27.5 (34wk), 15.6 (35wk), 1.5 (37wk), 7.9 (38wk), 6.4 (39wk),
15 (40wk), 14.9 (41wk), 9.1 (42wk).

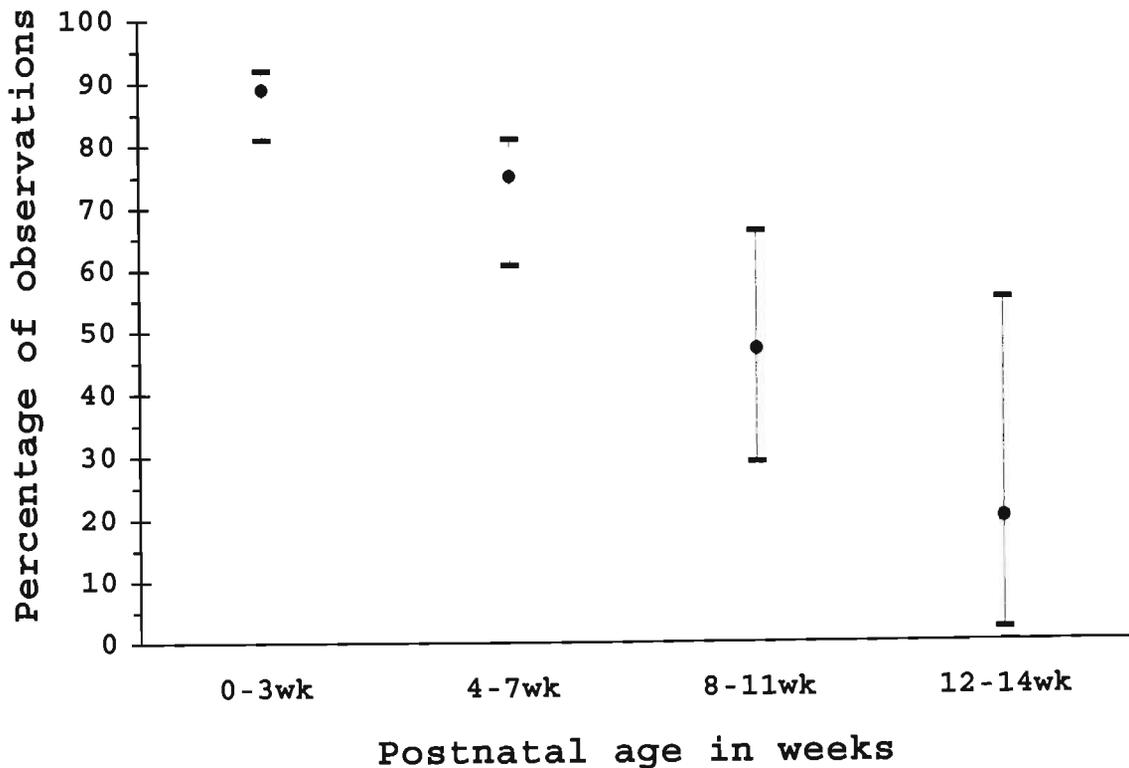


Figure 25
Presence of slow variability in CBFV related to postnatal age showing the percentage incidence and 95% confidence intervals

The pattern of evolution did not seem to relate to brain injury in the small group who sustained it except that, of the three who developed PVL, one was the only baby who never demonstrated slow variability; the others showed slow variations up to the time of discharge. In the 6 with PVH no particular pattern could be seen.

The disappearance of slow variations in CBFV could not have been due to truncation of the peak systolic velocity; the

automatic scaling within the software always allows the maximum velocity to be displayed.

Careful inspection reveals the appearance of slow variations in the diastolic velocity of cerebral blood flow. This was observed in 19 infants, generally after 31 weeks gestational age (Figure 15).

III.IV. Follow-up study

Of the 74 infants enrolled, 15 infants died, 13 before discharge and 2 later from sudden infant death syndrome. Three of the 59 survivors were lost to follow-up. The remaining 56 were seen and assessed by one Paediatrician (RM) at 18 months post-term. Six were neurologically impaired. Three had asymmetric spastic diplegia, 2 had spastic quadriplegia, and one had athetoid cerebral palsy. A further 3 had a Bayley mental developmental index below 70 and were classified as significantly developmentally delayed. There was no difference in the mean CBFV or blood pressure measured on any of the first 3 days between the normal survivors, neurodevelopmentally impaired survivors, or children who died (Table 14). However, when the trends over time were examined (Figure 26), those infants in the impaired group were less likely to show the usual steady increase in CBFV (Archer et al 1985, Fenton et al 1990). A rise, then a fall in CBFV occurred in 4 of 9 in this group (44%), whereas this pattern occurred in a smaller percentage (13%) of the group who were subsequently normal (4 of 31 of those with complete data). This difference was significant ($\chi^2 = 4.3$, $p=0.03$). The magnitude of the percentage increase between day 1 and day 3 was also smaller in the

abnormal group (Figure 27; median rise 0% vs 39%, Mann-Whitney $p= 0.03$). A correction for carbon dioxide tension was performed by expressing the CBFV in cm/sec per kPa of arterial CO₂ tension, but this did not alter these findings.

Table 14. Characteristics of infants followed to 18 months, mean cerebral blood flow velocity and mean arterial blood pressure measurements

	Normal	Delay/handicap	Died
<i>n</i>	42	9	15
Birthweight (g) (SD)	1245 (217)	1138 (263)	924 (228)
Gestation (wk) (SD)	29 (2)	27 (1.3)	26 (1.6)
Ventilated	36	9	15
Patent duct	3	2	1
Abnormal head ultrasound	1	6	6
Mean BP day 1 mmHg (SD)	43 (6.5)	44 (6.3)	33 (15)
Mean BP day 2 mmHg (SD)	48 (7.8)	43 (9.6)	43 (15.7)
Mean BP day 3 mmHg (SD)	51 (7.3)	44 (11.8)	36 (14)
Mean CBFV day 1 cm/sec (SD)	4.3 (2)	4.25 (1.25)	3.2 (1.65)
Mean CBFV day 2 cm/sec (SD)	6.5 (2.5)	5.7 (1.8)	5.6 (2.25)
Mean CBFV day 3 cm/sec (SD)	6.5 (2)	5.5 (1.9)	6.4 (3)

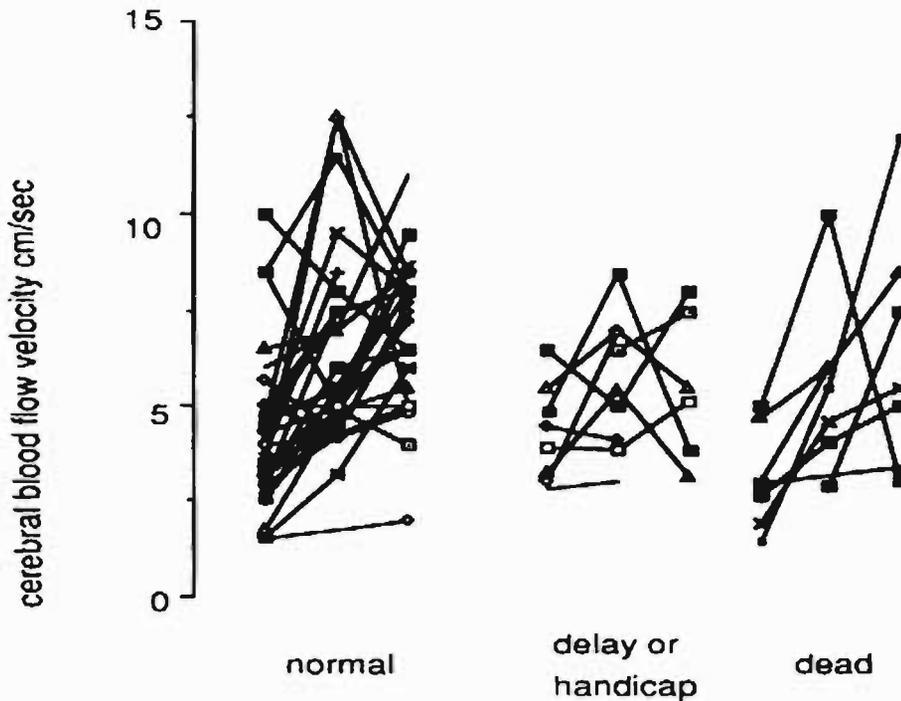


Figure 26 Cerebral blood flow velocity during the first 3 days of life shown in three groups according to outcome at 18 months

Six of the infants who were neurodevelopmentally abnormal had abnormal cranial ultrasound images in the neonatal period. Two had bilateral IVH with nonprogressive ventricular enlargement, one had a unilateral IVH, and one a parenchymal lesion present at birth, probably representing an infarction. Two infants had PVL, one unilateral and one with bilateral multiple cysts. Only one infant who was subsequently normal was considered to have any ultrasound abnormality in the neonatal period; this was described as bilateral small intraventricular haemorrhage without dilatation and a transient flare.

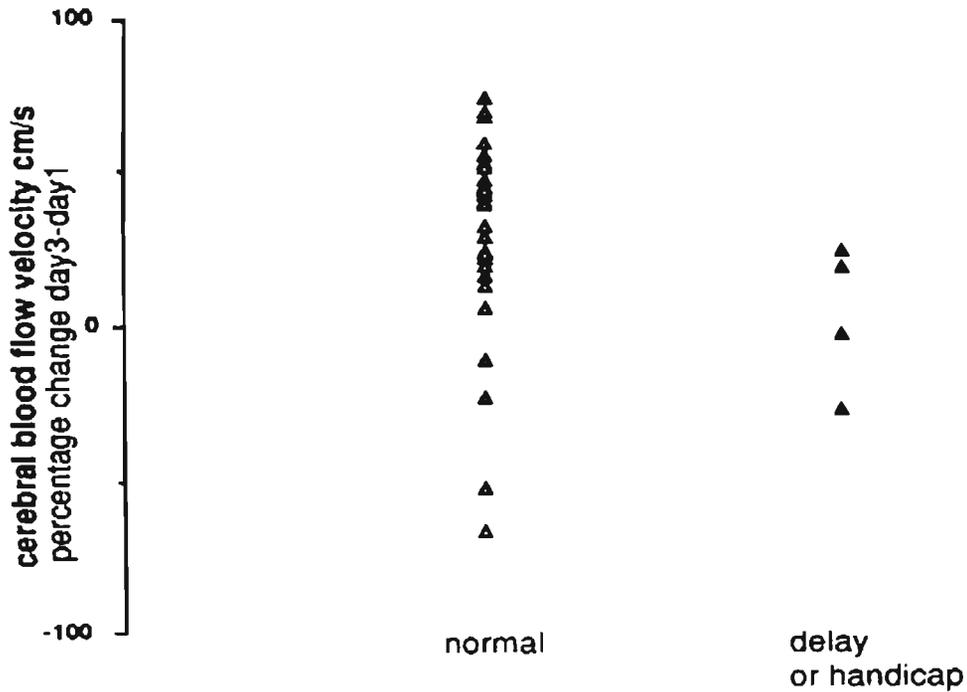


Figure 27 Percentage change in cerebral blood flow velocity between the third and first days of life: comparison between normal and handicapped infants

Table 15.
Results of measures of diagnostic performance for prediction of an abnormal neurological outcome

	Ultrasound Imaging	Doppler CBFV
	%	%
Sensitivity	66	44
Specificity	97	87
Positive predictive value	85	50
Negative predictive value	93	84
False-positive rate	2	13
False-negative rate	42	62
Efficiency	92	77

The sensitivity and specificity of ultrasound calculated from these results was 66% and 97%(Table 15), similar to the findings of Cooke(1987), in a larger cohort. Measures of diagnostic performance were also calculated for the "abnormal" CBFV pattern described(Table 15). Imaging proved a better predictor of outcome, with an overall efficiency(true positive + true negative/total number of patients) of 92% compared with 77% for the "abnormal" CBFV pattern.

Chapter IV. Discussion

IV.I. Study design

IV.I.I. Study validity

All parents approached agreed to their infant entering the study and no baby was withdrawn from the study once entered. This supports the accomplishment of minimal intervention with each baby. No infants were missed in the ten month period of collection.

A consecutive cohort was chosen to represent an overall population of infants weighing less than 1501 grams. Few previous reports concerning cerebral blood flow velocity have employed cohorts. No infant was excluded from the study on the basis of growth retardation and, during the recruitment period, no infants were delivered at a viable gestation with a lethal congenital malformation. No infant was excluded because of severity of illness and the cohort included several babies who were extremely sick, which was not always the case in other studies. Previous studies did not have simultaneous recordings of blood pressure, respiration and CBFV ie physiological monitoring.

IV.I.II. Timing of each study

As seen from Figures 10 and 11, the equipment used was extremely bulky. Many of the infants involved were very sick and required minimal interventions. Daily studies were the maximum permissible given the ethical requirement for minimal handling. For the same reason, the study had to be performed within a twenty-four hour period, but not at a specific time. This allowed essential procedures to be performed as necessary, ward rounds to proceed uninterrupted etc.

To obtain more information concerning slow variations in CBFV, consideration was given to measuring cerebral blood flow velocity in babies who were already home, or transferred to a unit closer to home, but this was impracticable.

IV.I.III. Duration of each study

Few previous studies had used recordings lasting as long as a minute. Rennie et al(1987, 1989) examined variability in CBFV in recordings of 10 successive cardiac cycles, ie approximately 7 seconds of data, while Perlman et al(1983, 1985) and Kuban et al(1988) studied 20 successive waveforms. Anthony et al(1991) then recorded CBFV continuously for a period of one minute using a transducer placed over the MCA. Only once longer recordings(ie a minute or longer) could be made was it possible to look at fluctuations other than beat-to-beat in CBFV. Our major interest, however, was in observing the frequency of a respiratory signal in the CBFV trace.

Anthony et al(1991) also drew attention to the fact that the presence of slow oscillations may lead to the misinterpretation of beat-to-beat variability in short recordings. The findings of this research support this, and further work is needed to clarify how long a recording must be to give accurate representation. The Nyquist limit dictates that if the frequency of cycling is one per minute, then two minutes is the minimum time required to allow representation of frequency.

At the time this study was performed, technological limitations of the equipment used precluded longer recordings of CBFV data. The memory buffer of the computer became full after 53 seconds of data since a high sampling rate(every

6.25msec) was important. Because recordings in this study lasted just under a minute, oscillations in the low and very low frequency ranges may have been missed.

Since then, technology has made significant progress. This has required new software for recording and analysis procedures, as well as the use of a fixed probe for recording CBFV. Such a probe has been employed in recordings from the middle cerebral artery in neonates (Anthony et al 1991), and recently, recordings over a 5 minute period have been reported (Panerai et al 1995, Reynolds et al 1997). These studies also confirm the presence of slow cyclical variations. Recordings have been made from the middle cerebral artery both continuously over a five minute period (Panerai et al 1995), and intermittently for five to twelve minute periods using continuous wave Doppler (Boylan et al 2000). Another group made recordings of CBFV of up to twenty-one minutes (Zernikov et al 1994). These same slow cyclical fluctuations at 3-5 times per minute have been seen where near-infrared spectroscopy was used to measure cerebral blood volume (Livera et al 1992).

IV.II. Critique

In the section dealing with the appearance of respiratory frequency in recordings of CBFV, the classification was based on the visual impressions of the author and one other (JR). In the absence of consensus the recording was not used in the results. Recordings from 4 infants were considered technically unsuitable. Although bias might have occurred on the part of the author, this is unlikely since all classification was carried out at the end of the study, and all recordings were assessed in one session.

Two hundred and forty nine recordings were analysed. Numbers, not names, were allocated to the traces prior to analysis to overcome the unlikely event that details of each case would be recalled during analysis.

In theory, confusion might arise where the heart rate was the same as, or a multiple of, the ventilator/respiratory rate, since the harmonics were indistinguishable from the frequency of interest. However this was not a problem in practice. The heart rate was never below 100/min(1.6Hz). The ventilator rate was generally 60-80 breaths/min(1-1.3Hz), although was occasionally above 100/min, the maximum being 150/min on one occasion. In addition, the heart rate frequency was always easy to distinguish since amplitude was always greater, and the signal less discrete than the signal at the respiratory frequency(Figures 12, 13). In our experience, respiratory frequency was always at a lesser Hz.

Visual examination of CBFV tracings to identify slow cyclical variation has been previously described(Anthony et al 1991, Michel et al 1994, Ferrari et al 1994). As Michel et al commented, "LF cycling can be easily detected by eye-balling". Processing data from 4-minute recordings of CBFV in normal newborns using the same microcomputer-based system as used here(Schlindwein et al 1989), Ferrari et al(1994) confirmed the findings of blinded visual classification of low frequency fluctuations with Fast Fourier Transform results.

As above, clinical data and identity of the infant were shielded from evaluation of the presence or absence of slow cycling. Four of the 133 recordings were unclassifiable.

IV.III. Examination of slow variations of CBFV in newborn babies

IV.III.I. Association of slow variations with degree of prematurity and outcome

This longitudinal study confirms the presence of slow variations in the CBFV of babies in the frequency range 1 to 5 cycles per minute as observed by others (Anthony et al 1991, Michel et al 1994, Ferrari et al 1994). This "cycling" variability is quite different from the beat-to-beat variability in blood pressure and CBFV described by Perlman et al (1983, 1985) and Mullaart et al (1992) and examined in the acute phase of this study.

Anthony et al (1991) described how these slow fluctuations occurred both in sick VLBW babies and in healthy term infants, and there was no evidence that they were harmful. Our studies confirmed and extended these findings.

In this study, the pattern of slow variability did not differ significantly between those without intracranial pathology and those with either PVH or PVL. The single baby who showed no slow variability had the most severe intracranial pathology of all babies studied. This would support the fact that slow variability is a normal phenomenon in newborn babies, absent only in cases of extreme pathology. This is endorsed by the findings of Reynolds et al (1997).

Up to the present time, of the three physiological variables HR, BP and CBFV, HR variability has been most studied. Reynolds et al (1997) found that an intact well-oxygenated central nervous system appears essential for normal HR variability. Their group showed a highly significant

difference in the low frequency band of CBFV between asphyxiated and normal babies, suggesting that low frequency oscillations would be more readily apparent in the normal than in the asphyxiated group. From their results, Reynolds' group also concluded that spectral analysis of CBFV adds further information concerning pathophysiological states than can be gleaned from standard CBFV estimations, or from spectral analysis of HR or BP alone. This was supported by Ferrari et al(1994). Looking at respiratory traces, they could identify no clear slow cycling at the frequency of interest either on visual inspection or on Fourier Transform. They found that the power of the resolved frequency from changes seen in CBFV was greater than that occurring in HR alone.

As declared by Reynolds et al(1997) "Whether the absence of oscillations or a shift toward the very low frequency region of the spectra indicates lack of or loss of autoregulation remains to be studied".

Longer studies examining CBFV, BP, HR and perhaps thermal stimulation might give further insight into the various components of low frequency spectra - how they interact and their role in physiological regulation.

In this study, slow variability occurred in the majority of very low birthweight infants in the first weeks of life, being recorded at least once in 29 of the 30 babies. It appeared to be independent of the presence of respiratory distress syndrome and of severity of illness, since some of the infants required no respiratory assistance while others required early inotropic support and ventilatory assistance for up to 44 days.

Similarly, administration of pancuronium, fentanyl or morphine in seven babies did not affect the presence of slow variations. Since this part of the study included only babies still in the nursery at 4 weeks of age, it excluded early neonatal deaths. Also, although the study infants were entered from a consecutive cohort of babies of birthweight less than 1500gm, those still present by 2-3 months all had chronic lung disease so were a very selected group.

IV.III.II. Evolution of slow variations with increasing postconceptional and postnatal age

The present study also suggests postnatal evolution of slow variability in CBFV. Early studies recording CBFV in adults for up to 10 minutes do not report the presence of slow variability except in REM sleep (Ellingsen et al 1987, Hauge et al 1980), suggesting that at some point of postconceptional age this becomes so damped as to be undetectable.

More recently, Newell et al (1992) found phasic variations (0.5-2 cycles per minute) under normal conditions as well as in pathological states. Mautner-Huppert et al (1989) found the same slow fluctuations in 8 of 10 patients described as healthy; however, in only 3 were the oscillations seen throughout the trace.

Ferrari et al (1994) found that the average percentage amplitude of such slow fluctuations in CBFV differed significantly within subjects for quiet versus active sleep. There was also a small change in cycle frequency which was statistically but probably not clinically significant. They suggested that these fluctuations represent an autoregulatory

process in the normal brain, and almost certainly reflect changes in the size of pial arteries.

Michel et al (1994) dispute that slow variability in the CBFV disappears with either postnatal or postconceptional age. They found neither frequency nor amplitude to diminish, but they studied only 15 babies whose gestational ages varied from 26 to 40 weeks. The postnatal age varied from 0-14 weeks but only 1 infant was more than 7 weeks old (14 weeks), and the median age was 3 weeks. However, because their study was of 10 minutes duration, and in our study slow variations were sometimes present for only part of the minute recorded, it is quite possible that recordings of a much longer duration would detect such variations until a much later postnatal and postconceptional age than we were able to.

Reynolds et al (1997) studied 2-15 minute recordings taken from the MCA with a CW probe. They demonstrated three frequency bands; at 0-0.02 Hz, 0.02-0.08 Hz and 0.08-0.5 Hz and found the same oscillations at 1-5 cycles per minute. This group's findings were in agreement with the study under review, in that slow cycling appeared to diminish with increasing postnatal age but they did not find this to be true of increasing gestational age. Again, this may relate to the short duration of recordings in my study.

In adults (Hyndman et al 1971, Kitney 1974) and term newborn infants (Schechtman et al 1989), slow variations are thought to be influenced by both thermoregulation and by baroreceptor reflex control mediated by the autonomic nervous system, and this may also be true for the preterm infant (van Ravenswaaij-Arts et al 1990).

It has long been known that noradrenaline is predominant over adrenaline in the neonatal period. Adrenaline is normally absent from the fetal adrenal, and under physiological conditions one would not expect an elevation of adrenaline in the neonatal circulation. However, Cheek et al(1963) found that 12 premature infants with RDS showed a significant and fourfold increase in adrenaline concentration and a non-significant increase in the level of noradrenaline, in comparison with premature infants who did not have RDS. Thus in severe RDS, increased baseline heart rate and decreased variability may result from an increased level of circulating catecholamines which may represent abnormally high sympathetic activity.

Bignall et al's work(1988) used spectral analysis of waveforms of both blood pressure and CBFV to demonstrate frequency components of variability of 0.5-1.5 Hz(respiratory rate), 1.5-3 Hz(heart rate) and 0.01-0.15 Hz(thermoregulation and baroreceptor modulation). Work in adults and in animals has also shown that variability is influenced by thermoregulation, and by pharmacological manipulation of the parasympathetic and sympathetic nervous systems. The renin-angiotensin system has also been shown to play a significant role in short-term cardiovascular regulation, and blocking this system increases the amplitude of very slow cycles(0.04 Hz) in dogs(Akselrod et al 1981).

High variability in the region of vasomotor influence(0-0.1 Hz) relative to that in the region of respiratory frequency (0.25-1.0 Hz) is suggested to be a risk factor for Sudden Infant Death Syndrome and may represent slow maturation of the

autonomic nervous system, with relative over-representation of the parasympathetic element (Kitney et al 1984, Schechtman et al 1992). In the group of premature babies studied here, the reduction in amplitude of slow variations with increasing age, may represent a maturation of the balance between the two components of the autonomic nervous system.

In this study, the cycle length of slow variations was variable, suggesting that several low frequency components were represented, but the recording time was limited to just under 1 minute by the computer software. Much longer recordings would be required to resolve the frequencies of several very slow variations with any degree of accuracy. It is of interest that Michel et al (1994) did not distinguish separate components within this frequency band despite recordings lasting 10 minutes.

The significance of slow cycling in the diastolic velocity which appeared later in gestation in just over half of the babies has yet to be explained. This same diastolic fluctuation is apparent in the traces from normal newborns in both active and quiet sleep, recorded by Ferrari et al (1994).

IV.IV. Cerebral blood flow velocity variability in the first week of life

IV.IV.I. Respiration induced variability in CBFV

The explanation which has been proposed for the origin of high variability in cerebral blood flow velocity, and which has been confirmed by several workers (Perlman et al 1983, Cowan et al 1987), is that the changes are similar to those of pulsus paradoxus seen in the systemic circulation. Pulsus paradoxus is usually recognised as a variation of blood pressure

occurring at the same frequency as respiration. This is a normal phenomenon when the direction of change is such that there is a small decrease in blood pressure with inspiration, and the magnitude of the change is less than 10mm Hg in adults. During inspiration, intrathoracic pressure falls and blood returns from the systemic venous circulation to the right side of the heart, giving an increased output from the right ventricle. The drop in intrathoracic pressure also allows dilatation of the pulmonary venous system so that a decreased amount of blood returns to the left side of the heart, leading to a fall in systemic blood pressure. In synchronous ventilation, the regular changes which occur during inspiration and expiration continue, with pulse volume and blood pressure falling during inspiration. Asynchronous ventilation generates negative intrathoracic pressure during inspiration, and hence pressure changes vary from exaggerated negative to exaggerated positive, with resultant variation in left ventricular stroke volume. Paralysis removes spontaneous respiratory effort, so changes in intrathoracic pressure and systemic BP reflect ventilator settings.

This study has confirmed that in a consecutive cohort of VLBW infants, pulsus paradoxus was present in the cerebral circulation at some time in more than half of the infants. Pulsus paradoxus is thought to be due to a central modulation of the baroreceptor reflex either by a direct neural communication from the respiratory centre or via thoracic volume receptors. The same phenomenon is responsible for respiratory sinus arrhythmia, and the amplitude of both these changes is increased when respiration occurs at or near the

natural oscillating frequency of baroreceptors (about 0.1 Hz in adults).

Previous work has shown that respiratory arrhythmia exists in the heart rate of newborn infants, albeit with a lower power than in adults (Giddens et al 1985). The smaller effect of respiration on the heart rate in newborn infants is thought to be due to the larger difference between the spontaneous respiratory frequency (0.4 Hz) and the natural baroreceptor oscillation frequency (0.1 Hz), making entrainment less likely than in adults where the two frequencies are closer. Giddens and Kitney (1985) also described a computer model of sinus arrhythmia and showed that a longer delay time of 3.3 seconds was necessary to stimulate the neonatal condition than that needed for adults (two seconds). The observations seen in the present study therefore seem unlikely to represent solely the respiratory entrainment of baroreceptor activity, as the frequency at which respiration was occurring was higher than that usually considered to be the natural baroreceptor oscillating frequency. It may be however, that artificial respiration at a similar frequency to natural respiration was sufficient to cause entrainment of a central oscillator or to set up an influence of its own.

van Ravenswaaij-Arts et al (1995) found that in the preterm infant, a fluctuation in HR occurs synchronously with artificial as well as with spontaneous ventilation. The influence of artificial ventilation on HR is not obviously reversed as was found in adults by Yli-Hankala et al (1991). This would support the concept of entrainment of a central respiratory activity by artificial ventilation in VLBW infants.

Such entrainment by periodic lung inflation has been described in humans and in animals (Muzzin et al 1986, Graves et al 1986), mediated through stretch receptors in the lung. So RSA in ventilated infants may mimic normal RSA, and be predominantly initiated by the central respiratory centre. This explanation does not require that a failure of autoregulation existed, allowing direct pressure transmission of changes in aortic blood pressure to the cerebral vessels. The fact that the respiratory transmission to CBFV was commonest in the smallest sickest infants, however, would suggest a relationship to impaired autoregulation.

Aarima et al (1988) found ventilator-induced RSA in preterm infants with RDS. This decreased with increasing age. This is consistent with our findings that RSA was most commonly present in CBFV on day one of life and steadily decreased in frequency over the first week.

Here, respiratory associated variability was more likely to occur in the cerebral circulation of those infants of short gestation on the first day of life, and independently of gestational age in those infants who were ventilated in high oxygen concentrations.

The independent effect of oxygen was probably due to the severity of respiratory distress syndrome, though infants with stiff lungs have been shown to transmit less ventilator pressure to the periphery of the lung so that an alternative explanation perhaps invoking the effect of catecholamines or circulating oxygen itself, is required. Examination of the phase relation of the changes in the systemic and cerebral

circulations and the heart rate changes may clarify this further.

The 8 babies who demonstrated hypotension during the study period also showed respiratory induced variability (Table 8). The number of hours that hypotension persisted on that day was also relevant. Similarly, of the 21 babies who were ever hypotensive, 17 showed this respiratory influence (Table 9). Oxygen requirement and ventilator settings were also higher in those with respiratory induced variability. All these factors point to these fluctuations occurring most often in the CBFV and BP of the sickest infants. These findings reinforce the link previously suggested between high beat-to-beat variability and cerebral injury. The association with cerebral injury in this group was striking, with 12 of the 13 infants with cerebral injury showing respiratory associated variability, but the association was not independent of gestational age. Mortality was also associated with respiratory associated variability. There were 11 deaths amongst the 47 who showed this variability, whilst no baby in the other group died.

Perhaps in preterm humans, as in fetal lambs (Papile et al 1985), the resting mean arterial blood pressure lies close to the lower limit of autoregulation and this predisposes the infant to risk by entering the pressure passive zone.

Ipsiroglu et al (1996) found respiratory associated variability generated by the ventilator after induction of halothane anaesthesia in infants. Since halothane causes transient impairment of cerebral autoregulation, they assumed that entrainment of ventilated babies occurred mainly in

hypovolaemic (and thus hypotensive) patients with compromised autoregulation.

Certainly, studies suggest that cerebral autoregulation is not intact in preterm infants, even where the head ultrasound and electroencephalogram is normal (Boylan et al 2000), and that perhaps this is not so until 4-6 weeks post-term (Kohler et al 1997).

The severity of lung disease and degree of prematurity presumably predispose infants to impairment of autoregulation, but perhaps factors unique to the cerebral circulation also play a part (Reynolds et al 1997, Ferrari et al 1994).

The presence of respiratory-induced variations in BP and CBFV occurred approximately forty percent of the time over the first week of life in VLBW infants. This percentage is less than that of Bignall et al (1988) who found respiratory-associated variability in CBFV in 60% of recordings made of 16 infants of less than 33 weeks gestation, or that of Perlman et al (1983), where two thirds of ventilated VLBW infants showed such variability. The most likely reason for this lower incidence of respiratory variation in CBFV than was reported by the two previous authors is that we studied a consecutive cohort of babies, not a selected group who were particularly ill.

IV.IV.II. Cerebral autoregulation

Autoregulation of cerebral blood flow is a highly complex function, with contributions from the autonomic nervous system, metabolic, chemical and humoral components, as well as the intrinsic responsiveness of smooth muscle in vessel walls. The presence of a vasomotor centre and details of how this exercises control has been widely investigated but still

requires clarification. Whilst neurogenic and humoral mechanisms are thought to have a relatively minor role in regulation of cerebral blood flow under normal circumstances, it is possible that they are more influential during stress, where the vasculature is immature, or after paralysis (Fenton et al 1992). Absence or impairment of such autoregulation is frequently implicated in the aetiology of intracerebral damage in the VLBW infant, and many attempts have been made to assess the adequacy of cerebral autoregulation in the human newborn.

In the 1970s and 1980s Lou et al (1979, 1988) employed the Xenon clearance technique, Milligan et al (1980) used plethysmography, and others have applied Doppler studies of cerebral blood flow (Newell et al 1994, Aaslid et al 1989, Cowan et al 1988, Jorch et al 1987).

In the 1990s, attempts have been made to formulate models of cerebral autoregulation in an effort to better study this phenomenon. Panerai et al (1993) used data collected in this study to form a model of the instantaneous pressure-velocity relationship of the neonatal circulation. This was an early example of this group's study of cerebral autoregulation and low frequency oscillations in CBFV. This work is ongoing (Boylan et al 2000).

Anthony et al (1993) studied CBFV after changes in posture in neonates. A biphasic response, rather than uniphasic passive attenuation was considered to be consistent with autoregulatory behaviour and was found to increase with increasing gestational age. This technique can only be performed at irregular intervals and the duration of studies of autoregulation need to be long enough to be free from

inaccuracies in CBFV introduced by the presence of slow cycling as seen here and previously (Anthony et al 1991, Michel et al 1994, Ferrari et al 1994). Panerai et al (1995) therefore postulated that computerised coherent averaging of CBFV response to spontaneous small changes in blood pressure, may be a promising new method for noninvasive bedside assessment. Reynolds et al (1997) used continuous measurement of CBFV in the middle cerebral artery over 5 minute periods, to monitor cerebral blood flow. The time course for autoregulation, when present, was in agreement with that reported in adults, with similar changes in magnitude and time. Further studies of cerebral autoregulation certainly require longer recordings; In 1995, Panerai's group studied newborns for up to 15 minutes.

Many studies have concentrated on the relationship between arterial blood pressure and cerebral blood flow, showing that flow is maintained constant over a certain arterial pressure range (autoregulatory plateau) under ideal physiological conditions. Cerebral blood flow decreases as arterial pressure falls below that range, and increases as arterial pressures rise above that range. The time course for autoregulation has been described in adults, and has been shown to vary with the carbon dioxide level (Aaslid et al 1989). Arterial PaCO_2 is also known to be one of the most important mediators of cerebral blood flow, causing vasodilatation especially in the smallest pial vessels. Menke et al found the direct effect of PaCO_2 on CBFV to be approximately ten times that of PaO_2 on CBFV in preterm infants (1993).

Our study did not find that blood gas values altered cerebral blood flow velocity, but we did not manipulate either

PaO₂ or PaCO₂ levels, and so did not specifically observe the effect of altered blood gases on flow velocity. We do not believe that blood gas values altered significantly over the time of study and this was supported by transcutaneous gas monitoring in almost all infants.

Tweed et al(1983) demonstrated that intracerebral autoregulation is functionally developed over a range of arterial blood pressure in the mature fetal lamb but is lost in the presence of significantly reduced arterial oxygen concentration. Again, oxygenation was not manipulated in this study.

The strong similarity seen between the CBFV and arterial BP traces in this study, supports the premise that the preterm infant lacks adequate cerebral autoregulation. Although Cowan et al(1988) found significant association between what she considered absent or ineffective cerebral autoregulation and the development of haemorrhagic and/or ischaemic cerebral lesions, Gronlund et al(1994) found no association between short term variability in BP or HR, and the occurrence of peri/intraventricular haemorrhage.

Figures 18 and 19 show that in most instances where BP variability was high, so was that of CBFV; low CBFV in the presence of high BPV would support effective cerebral autoregulation. However, there were a few babies who demonstrated high CBFV where BPV was low, suggesting some intracerebral mechanism might be responsible, at least in part. The findings(Reynolds et al 1997) that CBFV recordings yielded more information than was available from analysis of BPV and/or HRV would support this. Mullaart et al(1992) claimed that

restlessness (rather than wakefulness) enhanced variability in CBFV, and Ramaekers et al (1989) have previously shown variations in CBFV to be more pronounced in non-REM sleep. Perhaps behavioural state had a role in this CBFV.

IV.IV.III. Relationship between CBFV and arterial BP, cerebral injury and outcome

Several groups believe that very high variability in CBFV may be indicative of adverse outcome and the present study, despite the small numbers, still lends support to this argument. Perlman et al (1983) found that babies at risk of cerebral haemorrhage had CV% values in CBFV of 16% to 47%. Rennie et al found a reduction in CBFV from a median of 13% to a median of 5% following cardiovascular support in a group of ventilated preterm infants in one study (1989), and a decrease from 11% to 5% after achieving synchrony of ventilation in another (1987). Our current range of maximum CV% on the first day of life (5 - 47%) is consistent with these studies. Bada et al (1990), found greater BP fluctuation for a longer proportion of time in infants less than 32 weeks gestation ventilated for RDS who did not develop IVH, than in those who did. They, as well as Miall-Allen's group (1989), suggested that a degree of variability was a sign of healthy physiology in babies. Cheek et al (1963) and Reynolds et al (1997) found loss of variability in the heart rate of a newborn baby to be a poor prognostic indicator.

Our hypotensive babies demonstrated significantly higher CV%'s in CBFV than their normotensive peers. Though there was also a strong association between adverse outcome and high CV% in CBFV, there was not a significant correlation between CV% in

CBFV, and cerebral injury. The use of inotropes in babies who were hypotensive may explain this at least in part. Also, not all events precipitating the injury, necessarily occurred on day 1 when the coefficient of variation of CBFV was measured. Some harmful events may have occurred in utero - one infant's mother had severe antepartum haemorrhage prior to delivery; in other infants, events such as pneumothorax occurred after the first day, when the data was collected for this part of the research. This is in accordance with increasing evidence in the literature that severe brain injury may result from a sequence of events including some which are antenatal, some around the time of delivery and some postnatal (Resch et al 2000, Leviton et al 1999, O'Shea et al 1998). Intrauterine infection especially, has been implicated amongst antenatal risk factors (Weindling 1995, Fujimoto et al 1994, Graziani 1992). In the current study, there was no obvious relationship between infection and WMD though numbers were small. However, although documented postnatal infections were recorded, details of maternal antibiotics and intrauterine infections were sometimes sparse, and infection may have occurred undetected.

Currently, no studies using reliable measures of CBF have in fact demonstrated improvement in cerebral oxygenation after blood pressure enhancement. Lundstrom et al (2000) evaluated the effects of volume expansion compared with inotrope usage on BP, left ventricular output (LVO) and CBF (Xe clearance). They found that both volume expansion and low dose dopamine increased LVO, that dopamine but not volume reliably increased BP, but that neither inotrope nor volume expansion influenced CBF. Dopamine receptors have been found in both extracerebral

and intracerebral vessels (Seri 1995), but it is not known whether any of these are fully developed in the preterm infant. One self criticism of Lundstrom's study was that the confidence intervals were so wide that a small but clinically significant effect of dopamine on CBF could not be excluded. Also, no infant had severe hypotension, all mean BP's were 29-40mm Hg. Dopamine may have significantly altered CBF in the presence of more extreme hypotension.

In accord with their previous findings, Meek et al (1999) recently demonstrated that low CBF is a risk factor for severe IVH; in their study, infants developing IVH had a higher mean BP, indicating along with others that MABP is not necessarily a good indicator of cerebral perfusion (Osborn et al 2002, Kluckow et al 2001).

Mullaart et al (1994) found no significant difference in CBFV measured before and after the onset of periventricular haemorrhage, and questioned whether the variability in CBFV in fact plays a role in the aetiology of haemorrhage, or whether the two are merely coincident, both occurring in association with respiratory distress syndrome and a patent ductus. They suggested that this might be clarified by recording CBFV before and after surfactant administration for RDS. However, evidence is conflicting as to whether the actual process of administering surfactant increases (van de Bor 1991) or decreases (Cowan et al 1991) BP and CBFV.

It is interesting that our results support Perlman's findings (1983) of high variability in association with intracerebral haemorrhage, despite the consideration that the earlier study evaluated a very much shorter time interval (20

cycles, or approximately 9 seconds), and might have been influenced by the presence of "slow waves" (Anthony et al 1991, Bignall et al 1988, Coughtrey et al 1992).

The correlation between outcome and CV% in CBFV would suggest that large variations in CV% in CBFV may be a predictor of an unfavourable prognosis, even though CBFV per se does not seem to be. One interpretation of these results is that extremes of CV% in CBFV in preterm infants occur in those with least effective cerebral autoregulation, and thus who are most susceptible to intracranial injury and a poor outcome.

IV.IV.IV. Relationship between variability of CBFV, presence or absence of a patent ductus, and sedation

CBFV of preterm infants has been shown to vary beat by beat and minute by minute. Based on the findings of Perlman et al (1983), beat-to-beat variability in blood pressure was considered to be respiratory in origin. A high variability in CBFV shown with Doppler ultrasound in 23 of 50 ventilated infants was associated with ICH in 21. By paralysing infants, they reduced variability in arterial BP and in CBFV variability with resultant reduction in intracranial pathology.

Unlike Perlman et al (1985), we did not find that sedation or paralysis reduced variability, but in our group a concerted effort was made to achieve synchronous ventilation, and this succeeded 77.4% of the time. This technique was described by South and Morley in 1986, both "rate matching" the infant and ventilator, and also achieving "phase synchrony".

Unlike Mullaart et al (1994), who found that CBFV was promoted by ductal patency, we found no significant association

between the presence of PDA and high variability. Mullaart et al also used the presence of turbulence in the main pulmonary artery to diagnose PDA, so their methodology is subject to the same criticism as in this study. The incidence of PDA here was lower than generally reported for such a population during the years of study, and the method used for diagnosis may in fact have missed the presence of some ducts.

IV.V. Predictive value of cerebral blood flow velocity in VLBW infants

That parenchymal lesions are of far greater significance with regard to neurodevelopmental outcome than are haemorrhages confined to the ventricles is now widely accepted. The predictive value for outcome of cranial ultrasound demonstrating haemorrhage, even a very large haemorrhage, remains disappointing, but the presence of severe bilateral occipital cystic leucomalacia is almost always associated with a very poor prognosis (de Vries et al 1988, Jorch 1993).

Rennie et al (1995) followed infants from the cohort under discussion, to see whether supplementing cerebral ultrasound with studies of cerebral blood flow velocity in the form of Doppler, added further predictive insight. This in fact was not the case, and these results support the previous lack of correlation between CBFV measurement and ultrasound evidence of brain injury shown by Levene's group (Fenton et al 1992, Archer et al 1986). However, infants from this cohort with abnormal neurological signs or developmental delay, did not show the usual steady rise in cerebral blood flow velocity in the first few days of life, and the magnitude of the percentage increase between day 1 and day 3 was significantly smaller in the

abnormal group(Figure 27). This lack of rise in CBFV in the first few days in some infants who were abnormal was interesting and might reflect uncoupling of the metabolic demand with energy supply to the brain. However, this pattern was also seen in 4 infants who had a normal outcome, so results would need confirmation before any inferences could be made.

In this study, the overall incidence of intracranial haemorrhage was 24.3%, that of grade 3-4 intracranial haemorrhage 13.5% and that of periventricular leucomalacia 2.7%. Total numbers are obviously small, but the results are in line with others. Mortality to discharge was 17.6%. The Vermont Oxford database from 1990(1993) gave an NMR of 15% in VLBW infants. Current literature gives figures for survival to discharge of 91.5% for 1999(Donoghue et al).

No baby in the current group showed periods of hypertension. Recent studies however, suggest that elevated arterial blood pressure may be associated with periventricular or intraventricular haemorrhage(Gronlund et al 1994, Tyszczyk et al 1995). Tyszczyk's group used near infrared spectroscopy to measure cerebral blood flow in infants of 24-32 weeks gestation whose mean arterial blood pressure was either above or below 30mmHg - the minimal value claimed necessary to maintain cerebral perfusion in very low birthweight infants(Bada et al 1990). There was no significant difference in cerebral blood flow between the two groups of infants. One of 13 infants in the group with mean arterial pressure above 30mmHg developed intraventricular haemorrhage whilst there was no haemorrhage in the other group(total number 11); however, one infant in the group where the mean BP was not maintained above 30mm Hg did

develop periventricular leucomalacia, the only case of this seen. No information was given concerning inotropic use in that study. Determining the "ideal" blood pressure for each VLBW infant remains a major problem which cannot be resolved without consideration of other organ function. The results presented in this thesis lend further weight to the mounting evidence that adequate cerebral perfusion is an important factor in preventing preterm brain injury.

IV.VI. Conclusions

IV.VI.I. Key messages

Slow variability in CBFV seems to be a normal phenomenon occurring in most VLBW infants in the first week of life. This seems to be independent of severity of illness, sedation or inotropes.

Slow variability evolves with increasing postnatal and post gestational ages and may reflect maturation of the autonomic nervous system.

It is probable that several low frequency components were represented in the slow variability. Longer recordings might clarify this.

Respiratory induced variability was present in the cerebral circulation at least once in over half of the cohort of 74 VLBW infants. Infants who showed respiratory associated variation were smaller, less mature, and more likely to be ventilated using a higher peak pressure, rate and inspired oxygen concentration. They were more likely to die or sustain brain injury than those who never showed such a variation in their brain blood flow. There were more infants who were hypotensive at any time in the respiratory associated variability group.

There was a strong correlation between variability of CBFV and that of arterial BP.

Babies who had episodes of hypotension had significantly higher variability of CBFV than did those who remained normotensive.

The correlation between coefficient of variation of CBFV and outcome suggests that either extreme of variability in CBFV may predict an unfavourable outcome.

Extremes of CV% in CBFV may occur most often in those infants with the least effective cerebral autoregulation.

Neither sedation nor paralysis influenced CV% of CBFV in this study, but "rate matching" and "phase synchrony" were constantly undertaken.

Supplementing cerebral ultrasound imaging with Doppler studies of CBFV does not add further predictive insight.

IV.VI.II. Summary of publications and presentations resulting from this research

IV.VI.II.I. Publications

Coughtrey H, Rennie J, Evans DH 1997 Variability in cerebral blood flow velocity: observations over one minute in preterm babies. **Early Hum Dev 47:255-60.**

Rennie JM, Coughtrey H, Morley RM, Evans DH. 1995 Comparison of cerebral blood flow velocity with cranial ultrasound imaging for early prediction of outcome in preterm infants. **J Clin Ultrasound 23(1); 27-31.**

Coughtrey H, Rennie JM, Evans DH, Cole TJ. 1993 Factors associated with respiratory induced variability in cerebral blood flow velocity. **Arch Dis Child 68 ; 312-6.**

Panerai RB, Coughtrey H, Rennie J , Evans DH. 1993 A model of the Instantaneous Pressure-Velocity Relationships of the Neonatal Cerebral Circulation. **Physiol-Meas 14 (4); 411-8.**

Coughtrey H, Rennie JM, Evans DH. 1992 Postnatal evolution of slow variations in cerebral blood flow velocity. **Arch Dis Child 67 (4); 412-5.**

Coughtrey H, Rennie JM, Evans DH. 1991 Patterns of cerebral blood flow velocity variability in premature babies. **Excerpta Medica International Congress Series.**

Coughtrey H, Rennie JM, Evans DH. 1991 Factors influencing the transmission of respiratory-induced variation in blood pressure to the cerebral circulation. **J Maternal-Fetal Investigation 1;100.**

IV.VI.II.II. Presentations at Meetings

Rennie JM, Coughtrey H, Morley RM, Evans DH. October 1992 Comparison of cerebral blood flow velocity with cranial ultrasound imaging for early prediction of outcome in preterm infants. **Symposium on fetal and neonatal neurology, Tours.**

Coughtrey H, Rennie JM, Evans D. August 1991 Factors influencing the transmission of respiratory-induced variation in blood pressure to the cerebral circulation of preterm babies. **4th Congress of the International Perinatal Doppler Society, Malmo.**

Coughtrey H, Rennie JM, Evans D. May 1991 Patterns of cerebral blood flow velocity variability in premature babies. **4th International Conference on Fetal and Neonatal Physiological Measurements, Rotterdam.**

Coughtrey H, Rennie JM, Evans D. February 1991 Postnatal evolution of cyclical variations in cerebral blood flow velocity. **Neonatal Society, London.**

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Appendix 1. Data sheet

Baby Number

Hospital Number Name DOB

Maternal Age LMP EDD

Maternal medication Parity Gravidity

Maternal medical history

Pregnancy history

Labour Y/N

Labour complications

Mode of delivery: vaginal/cephalic

vaginal/breech

CS/elective

CS/emergency

other

At birth

 Apgar ¹ Apgar ⁵ Cord pH

Bwt Sex Gestation

Diet : Vamin

Intralipid Breast milk + phosphate

Osterprem Breast milk + other

Sepsis	Proven/suspected	
Antibiotics		
Ventilation	Duration IMV (days)	
	Maximum pressures	
	Duration CPAP (days)	
	Maximum pressures	Duration
	Maximum O ₂	Duration
	Maximum rate	Duration
	Days in O ₂	
Surfactant given	Y/N	Times given
CXR diagnosis		
Umbilical arterial catheter	Y/N	Peripheral arterial line Y/N
Duration mean BP < 30mm (total hours)		

STUDY	DAY 1	DAY 2	DAY 3	DAY 7	DAY X
Ventilation					
PIP					
rate					
FIO ₂					
Pneumothorax					
PIE					
P'mediast					
Reintubation					
Sedation					
Pavulon					
Morphine					
Phenobarb					
Fentanyl					
Other					
Aminophylline Y/N					
Clinical PDA Y/N					
Doppler PDAY/N					
Indocid Y/N					
Hypotension Y/N					
Dopamine Y/N					
Dobutamine Y/N					
ABG during study					
pH					
pAO ₂					
pCO ₂					

BE

DAY 1 DAY 2 DAY 3 DAY 7 DAY X

Head U/S

Haemorrhage

Gde 0

Gde 1

Gde 2

Gde 3

Gde 4

Ventric Diln

0

transient

persistent stable

progressive

persist asym

Parenchymal

1=cyst commun

2=cyst sep ventric

3=IPH sep ventric

Prolonged flare

PVL

single

multiple

anterior

centrum ovale

posterior

Week	2	3	4	5	6	7	8	9	10	11	12	13	14
Ventilated	Y/N												
FIO ₂	Y/N												
Clinical PDA	Y/N												
Doppler PDA	Y/N												
Sepsis	Y/N												
Tolerating feeds	Y/N												

KEY

CPAP	Continuous positive airways pressure
CXR	Chest radiograph
Cyst commun	Cyst communicating with ventricle
Cyst sep ventric	Cyst separate from ventricle
IMV	Intermittent mandatory ventilation
IPH sep ventric	Intraparenchymal haemorrhage separate from ventricle
Persist asym	Persistent asymmetrical
PIE	Pulmonary interstitial emphysema
PIP	Positive inspiratory pressure
P'mediast	Pneumomediastinum
Ventric dil ⁿ	Ventricular dilatation

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